Procter&Gamble

The Procter & Gamble Company
Winton Hill Technical Center
6071 Center Hill Avenue, Cincinnati, Ohio 45224-1783

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March 3, 2000

Docket Management Office
5630 Fisher's Lane
Rockville, MD 20852

Dear Madam:

We wish to submit the enclosed report and cover letter entitled "Final Report - Cohorts 1 through 6 - Randomized, Double-Blind, Placebo Controlled Consumer Rechallenge Test of Olean Salted Snacks" to the olestra docket #00F-0792 so that it is publicly available. This report was previously submitted to Mary Ditto of FDA's Office of Pre-market Approval on January 30, 1998.

In addition, this information is available in the publication listed below which has already been submitted to the olestra docket: We attached another copy for your convenience.

> Zorich NL, Biedermann D, Riccardi KA, Bishop LJ, Filloon TG, Randomized, double-blind, placebo-controlled, consumer rechallenge test of Olean salted snacks, Regulatory Toxicology and Pharmacology 26, 200-209 (1997). Commentary on a follow-up to this study was also published in Regulatory Toxicology and Pharmacology 27, 2 (1998).

Please let me know if you have any questions (513-634-6808).

Thank you.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Greg Allgood, Ph.D.
Associate Director
Regulatory & Clinical Development

Enclosure

00F-0792

RPT 7

REGULATORY TOXICOLOGY AND PHARMACOLOGY 26, 200–209 (1997)
ARTICLE NO. RT971164

Randomized, Double-Blind, Placebo-Controlled, Consumer Rechallenge Test of Olean Salted Snacks

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Received July 19, 1997

Olestra is a zero-calorie fat substitute that is neither digested nor absorbed. A randomized, double-blind, placebo-controlled, within-subject, crossover rechallenge study was conducted to compare the occurrence of gastrointestinal symptoms after ingestion of chips made with Olean brand of olestra or conventional triglycerides in subjects who had previously experienced gastrointestinal symptoms they attributed to consuming Olean. A total of 57 male or female subjects received 2 oz of Olean potato chips or triglyceride potato chips at each of four weekly site visits. The occurrence of gastrointestinal effects after product consumption was noted in follow-up telephone interviews 3 to 5 days after each visit. There was no significant difference in the frequency of any gastrointestinal symptoms (abdominal cramping, diarrhea, loose stools) following consumption of Olean chips or triglyceride chips, and the severity of diarrhea, loose stools, and abdominal cramping was similar. We conclude that consumption of a 2-oz serving of Olean chips is no more likely to result in reports of gastrointestinal symptoms than consumption of triglyceride snacks as a part of the usual diet, even in individuals who have claimed intolerance to Olean. The data suggest that subjects who previously experienced symptoms that they attributed to consuming products made with Olean may have mistakenly attributed their symptoms to these products.

INTRODUCTION

Olestra (Olean brand, Procter & Gamble), a mixture of octa-, hepta-, and hexafatty esters of sucrose made by processes common in the fats and oils industry, is a nonabsorbable, noncaloric fat replacer. The Food and Drug Administration approved the use of olestra in savory snack foods (e.g., potato chips, corn chips, and extruded snacks and crackers) in January 1996 (FDA, 1996). Products made with olestra were initially marketed in April 1996. All products containing olestra are labeled with the Olean ingredient trademark and also display the following information statement: "**This Product Contains Olestra.** Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added." The product labeling refers consumers to a toll-free telephone number staffed by the Frito-Lay Co. or by Procter & Gamble, the manufacturers of products containing Olean.

In comparative studies in which individuals consumed olestra or triglyceride foods at every meal for 56 consecutive days, subjects who received higher levels of olestra reported a greater frequency of gastrointestinal symptoms than subjects who received conventional triglyceride (Schlagheck *et al.*, 1997a,b). These findings account for the presence of the current product information label whose purpose is to inform consumers who may be eating substantial amounts of Olean on a daily basis. However, subjects in these same studies who consumed olestra foods at the 90th percentile of expected chronic consumption (Webb *et al.*, 1997) did not report significantly more gastrointestinal effects than subjects who consumed conventional triglycerides. In addition, in other studies in which subjects consumed chips in single eating occasions or in typical snack-eating simulations, there was little to no difference in the frequency of reported gastrointestinal symptoms between subjects who consumed olestra chips and those who consumed conventional triglyceride chips (FDA, 1996; Cheskin *et al.*, in press; Koonsvitsky *et al.*, 1997; Zorich *et al.*, in press). Nevertheless, the marketing of olestra products has resulted in reports of effects that consumers have associated with consumption of olestra, even when the amounts of olestra products consumed have been limited. Between April 22, 1996, and January 26, 1997, 508 persons called Frito-Lay or Procter & Gamble to report effects that they associated with consumption of olestra products; about 95% of

[1] This study was funded by the Procter & Gamble Co., Cincinnati, OH.

0273-2300/97 $25.00

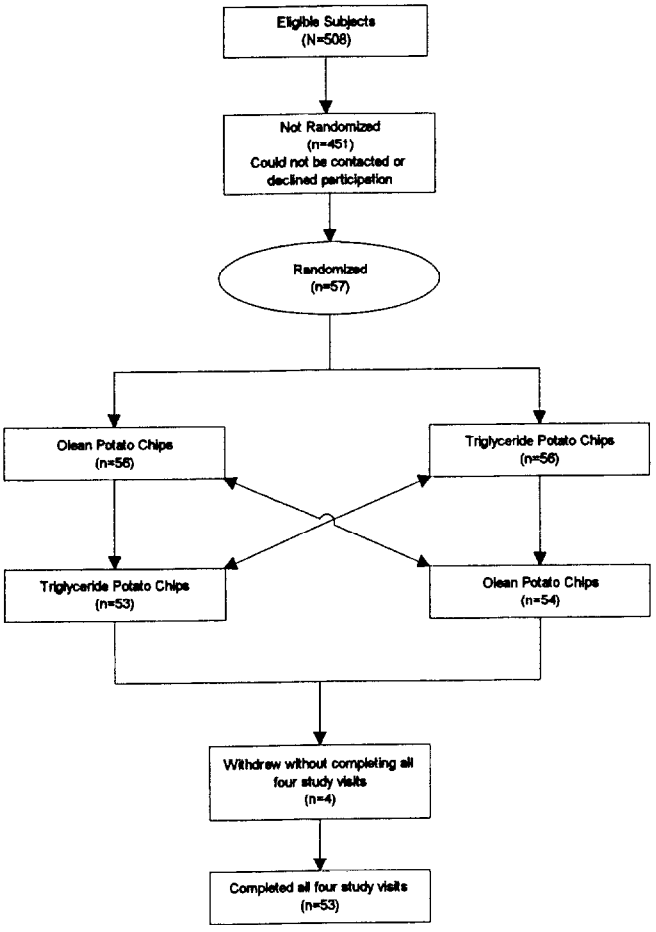

FIG. 1. Trial profile. The intervention treatments were Olean chips and triglyceride chips. In this crossover trial, subjects consumed Olean chips on two occasions and triglyceride chips on two occasions in random order, as determined by a balanced randomization scheme. Of the four subjects who withdrew, one withdrew after eating Olean chips on one occasion because she did not want to eat the requisite amount of chips; one withdrew after eating triglyceride chips on one occasion because she felt "uncomfortable" about participating; one withdrew after eating Olean chips on one occasion and triglyceride chips on one occasion because she received a mouth injury that limited her ability to eat chips; and one withdrew after eating Olean chips on two occasions and triglyceride chips on one occasion because he could not complete the fourth visit for personal reasons.

these effects were related to the gastrointestinal system.

We conducted a randomized, double-blind, placebo-controlled, four-period, within-subject crossover study to rechallenge consumers who called to report that they had experienced gastrointestinal symptoms that they attributed to eating snacks made with Olean (Fig. 1). The study compared the occurrence of gastrointestinal symptoms in these consumers after ingestion of chips made with Olean and after ingestion of chips made with conventional triglycerides. The objectives of the study were to gain a better understanding of the events that initially prompted the consumers to call and report their experience, to help consumers put their initial event into perspective, and to address whether reports of diarrhea, loose stools, and cramping from these consumers are associated with olestra consumption.

METHODS

Subjects

The study subjects were recruited from the 508 consumers who had voluntarily called Frito-Lay or Procter & Gamble between April 22, 1996, and January 26, 1997, and reported gastrointestinal symptoms that they associated with consumption of products containing olestra. During this initial voluntary call, subjects were asked to provide demographic information, a medical history, and a list of medications they were currently taking. In addition, they were asked which product they had consumed, how much of it they had consumed, and for how long. They were asked to describe the symptoms they had experienced; their onset, duration, and severity; and any treatment they had received. Subjects who reported diarrhea were asked about the frequency and consistency of their bowel movements while they were having symptoms.

Of the 508 subjects in the database, 86% claimed that consumption of Olean products resulted in diarrhea, loose stools, or abdominal cramping, and 40% rated one or more of their symptoms as severe, relative to symptoms they had experienced in the past. Thirty-five percent did not describe the severity of one or more of their symptoms. Of the subjects who indicated the number of times they consumed olestra chips before experiencing symptoms, 365 (79%) reported that they experienced symptoms after eating chips on a single occasion. Demographic data, the amount of Olean consumed, the adverse effects, and the severity of gastrointestinal symptoms reported during the initial voluntary call for the 508 subjects in the database are presented in Tables 1, 2, 3, and 4, respectively.

Subjects were ineligible to participate in the study if they were less than 2 years of age, if another household member was currently participating in the study, or if they had a physical or mental condition that would prevent them from completing the study procedures. (Household members of study participants were eligible for future enrollment.) Written informed consent was obtained for each subject before the study procedures were begun.

Fifty-seven subjects were enrolled in the study. The remaining 451 nonparticipating subjects could not be recontacted or declined to participate. Of the 57 study participants, 93% had initial complaints of diarrhea, loose stools, or abdominal cramping, and 40% rated

TABLE 1

Demographic Characteristics of Study Participants and All Subjects in the Database[a]

Parameter	Study participants (n = 57) No. (%)	Subjects in the database (n = 508)[a] No. (%)
Sex		
Male	15 (26)	198 (39)
Female	42 (74)	310 (61)
Age (years)		
0–5	0 (0)	39 (8)
6–11	1 (2)	32 (6)
12–65	48 (84)	361 (71)
>65	7 (12)	41 (8)
Unknown	1 (2)	35 (7)

[a] Database includes the 508 subjects who voluntarily called the manufacturer to report gastrointestinal effects that they associated with consumption of products containing Olean.

their symptoms as severe. Twenty-eight percent did not describe the severity of their symptoms. Seventy percent of the participants reported experiencing symptoms after eating chips on a single occasion. Demographic data, the amount of Olean consumed, the adverse effects, and the severity of gastrointestinal symptoms reported during the initial voluntary call by the 57 study participants are presented in Tables 1, 2, 3, and 4, respectively.

The protocol for the study was reviewed and approved by the Institutional Review Board of Procter & Gamble.

Test Product Administration

The study was conducted at four sites in areas in which Olean products were in test market (Eau Claire, WI; Cedar Rapids, IA; Grand Junction, CO; Columbus, OH). The study used the following four products: Frito-Lay MAX Ruffles potato chips made with Olean, Frito-Lay MAX Lay's potato chips made with Olean, Frito-Lay regular Ruffles made with conventional triglyceride, and Husman's regular potato chips made with conventional triglyceride. Two different Olean and two different tri-

TABLE 2

Amount of Olean Consumed before the Initial Voluntary Call by Study Participants and by All Subjects in the Database[a]

Amount of Olean consumed (g)	Study participants (n = 57) No. (%)	Subjects in the database (n = 508)[a] No. (%)
≤16.4[b]	34 (60)	297 (58)
>16.4–20	5 (9)	37 (7)
>20–51	15 (26)	112 (22)
>51	1 (2)	18 (4)
Unknown	2 (4)[c]	44 (9)

[a] Database includes the 508 subjects who voluntarily called the manufacturer to report gastrointestinal effects that they associated with consumption of products containing Olean.

[b] Equivalent to the amount of olestra in 2 oz of Olean chips.

[c] The amount of chips consumed was described as "many" for one of these participants and "a lot" for the other.

TABLE 3

Adverse Effects Most Frequently Reported by the Subjects in the Database[a] during the Initial Voluntary Call

Parameter	Study participants (n = 57) No. (%)[b]	Subjects in the database (n = 508)[a] No (%)[b]
Diarrhea	37 (65)	300 (59)
Abdominal cramping	30 (53)	285 (56)
Loose stools	8 (14)	75 (15)
Flatulence	9 (16)	69 (14)
Nausea	3 (5)	55 (11)
Bloating	5 (9)	32 (6)
Vomiting	1 (2)	25 (5)
Urgent bowel movement	3 (5)	24 (5)
Upset stomach	3 (5)	24 (5)
Stomach pain	1 (2)	20 (4)

[a] Database includes the 508 subjects who called the manufacturer voluntarily to report gastrointestinal effects that they associated with consumption of products containing Olean.

[b] Subjects may have been counted more than once.

TABLE 4

Severities of Diarrhea, Loose Stools, and Abdominal Cramping Reported during the Initial Voluntary Call

Symptoms reported during initial call	No. (%) of subjects with symptom: Study participants (n = 57)	Subjects in the database (n = 528)[a]
Diarrhea		
Mild	4 (11)	27 (9)
Moderate	9 (24)	84 (28)
Severe	13 (35)	103 (34)
Severity not reported	11 (30)	86 (29)
Loose stools		
Mild	2 (25)	13 (17)
Moderate	3 (38)	25 (33)
Severe	0 (0)	16 (21)
Severity not reported	3 (38)	21 (28)
Abdominal cramping		
Mild	5 (17)	36 (13)
Moderate	11 (37)	105 (37)
Severe	11 (37)	110 (39)
Severity not reported	3 (10)	34 (12)

[a] Database includes the 508 subjects who called the manufacturer voluntarily to report gastrointestinal effects that they associated with consumption of products containing Olean.

glyceride products were used to minimize the potential for unblinding due to product sensory attributes. Trained sensory panelists experienced with Olean could not identify which potato chips contained Olean within each pair of test products (MAX Ruffles and Ruffles; MAX Lay's and Husman's).

Each participant made four visits to the study site, at least 1 week apart, and received one of the four test products at each visit. During the study, every participant received each of the four test products (two Olean products and two triglyceride products) on one occasion. Participants received the test products in random order as determined by a balanced randomization scheme. Treatment sequences were assigned by the project biostatistician to subject numbers. The subject numbers were assigned to the study participants by personnel at each study site in the order in which the participants were enrolled in the study. Neither the study personnel, including the investigator, study monitor, data entry personnel, study physician, project physician, and study site staff, nor the study participants knew which participants were assigned to which treatment sequence.

Test products were purchased and repackaged in identical bags, each with 2 oz of chips (containing approximately 16.5 g of olestra or 20 g of conventional triglyceride). Like all marketed Olean products, the chips made with olestra contained vitamins A, E, D, and K, at levels specified in the olestra approval regulation (FDA, 1996). Each bag was labeled with ingredient lists for both the Olean and triglyceride potato chips, as well as the olestra product information statement. Prior to being served, the potato chips were poured into a bowl and weighed.

Before starting the study, participants were instructed to eat as much of the 2-oz potato chip serving as they could and to consume at least 1 oz of potato chips at each visit. In addition, they were asked to consume approximately the same amount of potato chips and to choose the same beverage at each visit. They were also asked not to consume any other Olean products while participating in the study. The study visits were conducted in comfortable surroundings with television and magazines available. The bowl of potato chips was placed on a tray along with the empty bag and served to the participants. The participants were allowed to eat as much of the chips as they desired over a period of 2 hr. If there were chips remaining, participants were asked if they could eat more but were not pressured to finish the entire 2-oz serving. In addition, participants were allowed to select a beverage from an assortment of regular cola, diet cola, regular lemon–lime soda, diet lemon–lime soda, or water. Consumption was monitored by direct observation and by weighing the test product before and after the consumption period. The amount of Olean or triglyceride consumed was calculated from the weight of the chips consumed, using analytical data on the percentage of Olean and the percentage of triglyceride in the chips.

Reporting of Symptoms

At the first visit, participants provided information on their general medical history and medication use. At each visit, before consuming the test products, participants were asked to list the foods they had consumed on that day and whether they were currently experiencing any digestive symptoms.

Participants were called 3 to 5 days after each visit and asked if they had experienced any digestive effects since consuming the chips earlier in the week. If the participants answered "no," they were asked questions about the acceptability of the taste and the product overall to ensure that the length of the call was similar to that for participants who reported symptoms. This measure was taken to avoid a "skip bias" in participants who might deny having symptoms in order to avoid more questions and a lengthy call. If the participants answered "yes," they were asked a series of questions to characterize the symptoms experienced and their time of onset, duration, and date of cessation. Participants were also asked to rate the severity of their symptoms as mild, moderate, or severe, according to the impact the symptoms had on their usual daily activities. Participants who reported symptoms were asked questions about food intolerances, medication use, and illness among household members. Participants could also report symptoms at the study site or call the study physician at the toll-free number provided to them. In each instance, the same information was collected.

Data Analyses

A sample size of 57 participants, with two measurements per treatment per participant, has greater than 85% power to detect a 15% increase in the occurrence of gastrointestinal symptoms with the assumptions that (1) the true occurrence of gastrointestinal symptoms after consumption of placebo is in the range of up to 15%, and (2) the responses across time for a given individual have little to no correlation.

After each product consumption occasion, participants were classified according to whether or not they had experienced gastrointestinal symptoms. A logistic regression analysis was performed to compare the occurrence of gastrointestinal symptoms during the periods following Olean and triglyceride consumption. Treatments were compared with respect to the frequency of each of the following gastrointestinal events: (1) any gastrointestinal symptom, (2) abdominal cramping, (3) diarrhea, (4) loose stools, (5) diarrhea or loose stools, and (6) gas (eructation, flatulence, bloat-

TABLE 5
Compliance with Chip Consumption

Percentage of two 2-oz servings consumed	Number (%) of Participants (n = 57)	
	Olean	Triglyceride
<50	4 (7)[a]	4 (7)[a]
50 to 75	9 (16)	12 (21)
76 to 89	12 (21)	7 (12)
>90	32 (56)	34 (60)

[a] Three of these subjects withdrew, and the fourth was noncompliant.

ing). Since this was a four-period, two-treatment, crossover study, the logistic regression model was stratified (by participant) and included terms for visit effects and treatment effects (Mehta and Patel, 1995). The treatments were declared to be statistically significantly different if the two-sided (Olean ≠ triglyceride) P value was ≤0.05. No adjustments were made to the P values even though there were multiple tests with respect to various gastrointestinal symptoms. Data from all participants who received the test products were included in the analyses except for gastrointestinal symptoms reported more than 5 days after the study visit.

RESULTS

Of the 57 participants enrolled, 53 completed the 4-week study. Three participants withdrew from the study: 1 because she did not want to eat the requisite amount of chips, 1 because she felt "uncomfortable" participating, and 1 because of a mouth injury that limited her ability to eat chips. A fourth participant completed only 3 weeks of the study because he could not complete the fourth visit for personal reasons.

Olean chips were consumed on 110 occasions and triglyceride chips were consumed on 109 occasions (53 participants ate each type of chip two times; 1 ate Olean chips once; 1 ate triglyceride chips once; 1 ate Olean chips once and triglyceride chips once; and 1 ate Olean chips twice and triglyceride chips once). All participants consumed at least 1 oz of chips at each visit except for the 3 participants who withdrew and 1 other whose compliance was poor at each of the four visits. Most participants consumed more than 90% of the two 2-oz servings of chips (Table 5). There was no difference between the two test products with regard to compliance.

Sixteen (28%) of the participants reported no symptoms during the study. As shown in Tables 6 and 7 and Fig. 2, there was no significant difference in the frequency of cramping, diarrhea, loose stools, diarrhea or loose stools, gas, or any gastrointestinal symptoms between the weeks following consumption of Olean chips and the weeks following consumption of triglyceride chips. The percentage of participants who reported diarrhea was higher after consumption of triglyceride chips than after consumption of Olean chips (8 and 4%, respectively), but the difference was not significant (P = .264). Conversely, the percentage of participants who reported gas was higher after consumption of Olean chips than after consumption of triglyceride chips (8 and 4%, respectively), but the difference was not significant (P = .203). There were also no apparent differences in the characteristics of the symptoms, such as severity, time to onset, or duration. No significant period effect on symptom reporting was observed for any symptom for any period in the study.

Reports of nongastrointestinal symptoms were uncommon. These included moderate headaches on several occasions, feeling shaky and dizzy, mild generalized rash, and traumatic injury to the mouth in one participant each, and upper respiratory symptoms in two participants.

Protocol deviations were minor and judged not to affect the outcome of the study. One participant consumed the test products out of the order specified by the balanced randomization scheme. Seventeen (8%) of the 218 postconsumption calls were made outside of the 3- to 5-day window specified by the protocol: 5 calls were made on Day 2, and 12 were made on Days 6, 7, or 8. In all cases, this was because participants were not available by telephone even though a specified time to contact them had been prearranged at the study site. Two reports of gastrointestinal symptoms were made more than 5 days after product consumption and were not included in the analysis. One participant reported that she felt queasy before consuming the test

TABLE 6
Occurrence of Gastrointestinal Symptoms after Consumption of Olean and Triglyceride

Occurrence of gastrointestinal symptoms	Number (%) of participants (n = 57)
No symptoms reported during the study	16 (28)
Symptoms reported after one eating occasion	
After one Olean-eating occasion	14 (25)
After one triglyceride-eating occasion	12 (21)
Symptoms reported after two eating occasions	
After both Olean-eating occasions	3 (5)
After both triglyceride-eating occasions	2 (4)
After one Olean-eating occasion and one triglyceride-eating occasion	6 (11)
Symptoms reported after three eating occasions	
After both Olean-eating occasions and one triglyceride-eating occasion	2 (4)
After both triglyceride-eating occasions and one Olean-eating occasion	2 (4)

TABLE 7

Number of Episodes and Severity of Diarrhea, Loose Stools, and Abdominal Cramping Reported by the 57 Study Participants during the Weeks Following Consumption of Olean or Triglyceride during the Study

	Olean				Triglyceride			
Symptom	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Diarrhea	3	1	0	4	4	4	1	9
Loose stools	4	4	0	8	8	1	0	9
Cramping	12	2	0	14	5	4	1	10

product at the Week 2 visit, and one participant reported that she had a stomachache on the morning of the Week 3 visit.

DISCUSSION

The goal of this study was to rechallenge individuals who had voluntarily called the manufacturer to report symptoms that they associated with consumption of Olean products. Of the 57 consumers who participated in the study, 53 (93%) had reported during the initial voluntary call that they had experienced diarrhea, loose stools, and/or abdominal cramping that they associated with consumption of Olean chips. The rechallenge study showed no significant difference in the frequency of cramping, diarrhea, loose stools, diarrhea or loose stools, gas, or any gastrointestinal symptoms between the weeks following consumption of Olean chips and the weeks following consumption of triglyceride chips. The percentage of participants who reported diarrhea was higher after consumption of triglyceride chips than after consumption of Olean chips, but the difference was not significant ($P = .264$). Conversely, the percentage of participants who reported gas was higher after consumption of Olean chips than after consumption of triglyceride chips, but the difference was

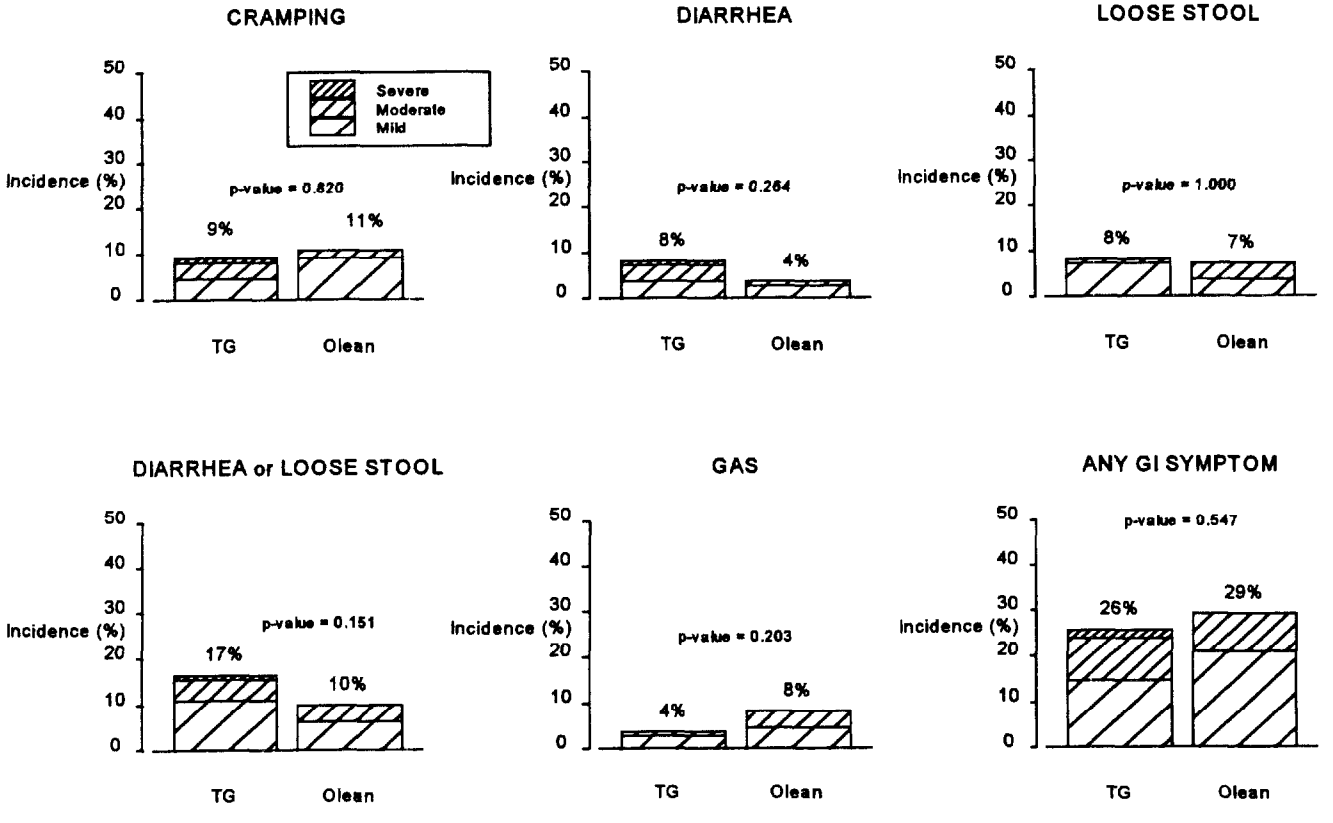

FIG. 2. Occurrence of gastrointestinal symptoms in 57 subjects after consumption of Olean chips (110 occasions) or triglyceride chips (109 occasions). TG, triglyceride.

not significant (P = .203). The severity and time of onset of the episodes of diarrhea, loose stools, and abdominal cramping reported during the study were similar following consumption of the Olean and triglyceride products. Thus, the response of these individuals to repeated exposures of chips made with Olean or triglycerides in a blinded fashion does not support an association of any clinically meaningful symptoms with Olean snack consumption under free-living conditions, even in a self-selected population.

The 57 participants in this study were representative of the database population of 508 consumers who voluntarily called Frito-Lay or Procter & Gamble to report an adverse effect that they associated with Olean consumption. The study participants were similar to the database population with respect to age and sex and with respect to the amounts of Olean consumed prior to the initial voluntary call. The study population was also similar to the database population with respect to the percentages of subjects who reported that consumption of Olean chips resulted in diarrhea, loose stools, or abdominal cramping; who rated their symptoms as "severe"; and who did not describe the severity of their symptoms. Thus, the group of subjects studied appears to be a representative sample of the population of interest.

Other studies in humans have also demonstrated little to no difference between the frequency of reporting of meaningful gastrointestinal symptoms after consumption of olestra chips or triglyceride chips in single eating occasions or in typical snack-eating simulations. In a recent, double-blind, randomized, parallel study, 1092 participants ate as much of a 13-oz bag of olestra chips or triglyceride chips as they wanted at a single eating occasion (Cheskin *et al.,* in press). There was no difference in the frequency of reporting of gastrointestinal symptoms overall or of any individual gastrointestinal symptom between subjects who consumed olestra chips and those who consumed triglyceride chips. In placebo-controlled studies, olestra was consumed in various foods at daily consumption levels of about 20 g/day (equivalent to 2.5 oz of olestra potato chips) for 16 weeks by 146 normal, healthy subjects (Koonsvitsky *et al.,* 1997) or for 4 weeks by 41 persons with inflammatory bowel disease (Zorich *et al.,* in press). In both studies, there were no differences between the placebo and olestra groups in the reporting rates of any gastrointestinal symptoms, including diarrhea or abdominal cramping, except for more reports of minor changes in stool frequency or stool character by subjects with inflammatory bowel disease when they ate foods made with olestra. Importantly, these changes were not characterized as diarrhea by these inflammatory bowel disease patients (Zorich *et al.,* in press).

The findings that consumption of olestra does not result in reports of gastrointestinal symptoms are consistent with the results of studies of the physiologic and morphologic effects of olestra in animals and humans. Such studies have demonstrated that olestra does not injure the gastrointestinal mucosa (Miller *et al.,* 1991; Lafranconi, *et al.,* 1994; Wood, *et al.,* 1991; Miller and Long, 1990) or result in malabsorption of carbohydrates, proteins, or fats (Lawson *et al.,* 1997). Further, olestra does not significantly alter fecal bile acid excretion (Glueck *et al.,* 1980; Crouse and Grundy, 1979), result in significant changes in gastrointestinal transit (Aggarwal *et al.,* 1993), or lead to significant alterations in stool water content (Bergholz, 1992; Fallat *et al.,* 1976). Olestra is not metabolized by the colonic microflora (Nuck *et al.,* 1994) and does not cause pathologic alteration in the colonic microflora (Eastwood and Allgood, 1995).

In this study, plain potato chips were selected as the best type of salted snack to use because they are available in the marketplace, they elicit good compliance, and they avoid the possible confounding ingredients present in corn chips or seasoned snacks. Consumption of products on two occasions provides information about whether the symptoms attributed to eating products made with Olean are reproducible and therefore possibly related to consumption of Olean, per se.

Use of a single standard serving size throughout the study allows data to be compared across subjects and study sites. The 2-oz serving was selected as an appropriate amount for this rechallenge study for two reasons: (1) this amount of chips has been shown to be a good approximation of the amount consumed by adults at a typical single eating occasion and (2) most of the individuals who called reported eating less than 2 oz (Table 2). In a study of the potato chip-eating behavior of 100 normal, healthy, lean and obese, male and female volunteers given free access to chips as a snack, the mean acute consumption of chips was approximately 2 oz (Miller *et al.,* 1995). In the recent study in which 1092 participants ate as much of a 13-oz bag of potato chips as they wanted, the median consumption of Frito-Lay MAX chips was 2.1 oz (Cheskin *et al.,* in press).

Comparison of the amounts of Olean consumed prior to the initial voluntary call and the amounts consumed during the rechallenge study showed that these amounts were comparable in nearly three quarters of the study participants. In 40% of the participants, consumption of 2 oz of chips (16.4 g of Olean) during the study resulted in ingestion of two or more times the amount of Olean that was originally stated to have caused their initial gastrointestinal symptoms. Despite the fact that the amounts of Olean consumed during the study were generally greater than or equal to the amounts that prompted the initial voluntary calls, the study provided no evidence that Olean chips were more likely to be associated with gastrointestinal complaints than triglyceride chips.

In this study, symptoms were monitored after a single eating occasion. This design was appropriate since 79% of the subjects in the database who indicated the number of times they consumed olestra chips before experiencing symptoms reported that they experienced symptoms after eating chips on a single occasion. This was consistent with the experiences of the 57 study participants, 70% of whom reported in their initial voluntary call that they experienced symptoms after eating chips on a single occasion.

A randomized, double-blind, placebo-controlled design was used for this trial because identifying the components of the diet that cause digestive symptoms is especially difficult. To prove a cause-and-effect relationship between an ingested product and ensuing symptoms, blinding must be effective so that subjects cannot distinguish between the putative offender and the comparative agent. As noted previously, two different Olean and two different triglyceride products were used to minimize the potential for unblinding due to product sensory attributes. The test product pairs were well matched with respect to appearance, taste, and texture as indicated by the fact that the members of a trained sensory panel experienced with Olean could not identify which potato chips contained Olean within each pair (Ruffles and MAX Ruffles; Husman's and MAX Lay's). In this study, the ability to identify the test products would have tended to bias the study findings against Olean since the study participants believed that consumption of Olean had caused them to have gastrointestinal symptoms in the past.

Identifying the cause of commonly occurring nonspecific complaints is difficult. This difficulty may lead to misattribution of symptoms to elements in the diet that are perceived to be associated with those symptoms. This problem is well illustrated in a study by Suarez *et al.* (1995), who conducted a randomized, double-blind, crossover trial of milk consumption in 30 people who reported that they had severe lactose intolerance. Reported symptoms included abdominal pain, bloating, flatulence, and/or diarrhea that occurred consistently after ingestion of even small amounts of milk. In the study, participants received 8 oz of 2% lactose-hydrolyzed milk or 2% milk plus an artificial sweetener (Equal) to correct for the change in taste (the strength of blinding was verified prior to the study). The investigators reported that there were no significant differences between the gastrointestinal symptoms reported after consumption of 2% lactose-hydrolyzed milk and 2% milk plus sweetener. In contrast, the reports of results of uncontrolled studies indicate that up to 60% of lactose-intolerant subjects had symptoms after drinking 8 oz of milk (Bayless *et al.*, 1975). The investigators concluded that people who consider themselves to be severely lactose intolerant may be misattributing their abdominal symptoms to lactose intolerance.

The reported association between aspartame and headache provides another example of possible misattribution of symptoms to food-product consumption. The widespread use of aspartame in the 1980s provoked a large number of consumer complaints, 517 of which were investigated by the Centers for Disease Control (CDC) (Butchko *et al.*, 1994). Over two thirds of these reports were of neurological/behavioral effects (mostly headaches), while most of the remainder of the reports (24%) were of common gastrointestinal complaints of abdominal pain, nausea, diarrhea, and vomiting (Council on Scientific Affairs, 1985; Butchko *et al.*, 1994). During this time, there had been considerable negative press about the safety and neurologic effects of aspartame consumption, which may have provoked the level of reporting (Butchko *et al.*, 1994). Schiffman *et al.* (1987) conducted a well-controlled, double-blind study in 40 subjects who had reported repeated headaches following the ingestion of products containing aspartame. The investigators found that the incidence of headaches after short-term challenge was equivalent to that after placebo. The CDC concluded that the symptoms being reported were generally mild and were symptoms that are commonly experienced by the general population (Butchko *et al.*, 1994).

The results of these studies with lactose and aspartame highlight the difficulties in determining the components of the diet that cause commonly occurring subjective symptoms. In these studies, subjects mistakenly attributed their symptoms to a substance that they believed would cause them problems or to a controversial food additive. These findings suggest that people tend to attribute commonly occurring subjective complaints, such as headaches and gastrointestinal complaints, to agents that others have found or stated to be a problem. Marketed Olean products bear an information label stating that olestra may cause abdominal cramping and loose stools. Because olestra is a nonabsorbed oil it is reasonable to expect that it could, if consumed in sufficient quantity over a sufficient period of time, produce a laxative-like effect in some individuals. Although dose-related mild-to-moderate gastrointestinal symptoms have been seen at some, but not all, of the dose levels studied in clinical studies in which subjects consumed olestra with every meal for weeks at a time (Schlagheck *et al.*, 1997a,b), data from studies conducted under typical snack-eating conditions indicate that people will not experience an increased occurrence of gastrointestinal symptoms when they eat olestra snacks (Cheskin *et al.*, in press; Koonsvitsky *et al.*, 1997; Zorich *et al.*, in press). Unfortunately, the current olestra label does not provide this perspective. The results of the study reported here, supported by the findings of Suarez, Schiffman, and their co-workers (Suarez *et al.*, 1995; Schiffman *et al.*, 1987), suggest that when consumers are given information (through label-

ing, the media, or other sources) that suggests a causative link between intake of a given substance and symptoms, consumers will report these symptoms at a high frequency, even when the circumstances of consumption render any cause-and-effect relationship outside of the range of reasonable biologic plausibility.

In our study, participants reported fewer and less severe symptoms following Olean consumption during the study than in their initial voluntary call. These findings, and also those of Suarez and Schiffman and co-workers (Suarez *et al.*, 1995; Schiffman *et al.*, 1987), suggest that people may tend to exaggerate their symptoms in an anecdotal setting and report them differently during a controlled study. Whether the symptoms that prompted the participants to make their initial voluntary calls were actually more severe than those that occurred during the study, or whether the participants were simply less likely to rate their symptoms as severe in a controlled testing situation cannot be ascertained from this study but is of interest.

In summary, in this study of 57 participants who had previously reported experiencing gastrointestinal symptoms that they associated with consumption of Olean products, there was no significant difference in the frequency of gastrointestinal symptoms after consumption of Olean chips or triglyceride chips. Although symptoms reported in the initial voluntary call were described as severe by 40% of the participants, none of the symptoms reported after olestra consumption during the study were described as severe.

CONCLUSIONS

We conclude that consumption of a 2-oz serving of snack made with Olean is no more likely to result in reports of gastrointestinal symptoms, including diarrhea, loose stools, or abdominal cramping, than consumption of snacks made with conventional triglycerides as a part of a usual diet, even in individuals who have claimed intolerance to Olean. Further, the results of this study suggest that the subjects who made the initial voluntary calls to the manufacturer may have mistakenly attributed their symptoms to products made with Olean.

ACKNOWLEDGMENTS

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COMMENTARY

Follow-Up to the Study: A Randomized, Double-Blind, Placebo-Controlled Consumer Rechallenge Test of Olean Salted Snacks

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Olestra is a zero-calorie fat substitute that is neither digested nor absorbed. We recently reported the results of a rechallenge study that compared the occurrence of gastrointestinal symptoms after ingestion of chips made with Olean brand of olestra or with conventional triglycerides in subjects who had previously experienced gastrointestinal symptoms they attributed to consuming Olean (Zorich *et al.*, 1997).

Follow-up studies have now been completed on 41 additional subjects, bringing the total number of participants to 98. The protocol called for enrollment of 100 subjects who voluntarily called the manufacturer to complain of gastrointestinal effects that they attributed to consumption of Olean products. From April 22, 1996, to June 5, 1997, 1134 consumers voluntarily called Frito-Lay or Procter & Gamble to report effects that they associated with consumption of products containing Olean. During the study, each participant made four visits to the study site and received 2 oz of either Olean or triglyceride chips. Participants were contacted 3 to 5 days after each study visit and questioned about whether they had experienced gastrointestinal symptoms after consuming the study product. The purpose of this commentary is to report the results of analyses of data from the complete study population of 98 subjects, which includes both the 57 subjects reported initially and the 41 subjects who have been enrolled since submission of the initial report.

For nearly three-quarters of the the study participants, the amount of Olean consumed in the rechallenge study was comparable to or greater than the amount associated with their initial call. Thirty-one percent of the participants reported no symptoms during the study, and there were no significant differences in the frequencies of cramping, diarrhea or loose stool, gas, or any gastrointestinal symptoms between the weeks following consumption of Olean chips and the weeks following consumption of triglyceride chips ($P > 0.20$). Although 48% of the participants described the symptoms that prompted their initial call as severe, only four (4%) participants reported severe symptoms upon rechallenge (all four after consuming triglyceride chips). The overall symptom severity ratings for all subjects were similar after consumption of Olean and triglyceride chips.

The results of the evaluation of these latest studies are consistent with those reported initially and with prior clinical experience with Olean. These findings demonstrate that consumption of a 2-oz serving of Olean chips is no more likely to result in reports of gastrointestinal symptoms than consumption of triglyceride snacks as a part of the usual diet, even in individuals who have claimed intolerance to Olean.

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Zorich, N. L., Biedermann, D., Riccardi, K. A., Bishop, L. J., and Filloon, T. G. (1997). Randomized, double-blind, placebo-controlled consumer rechallenge test of Olean salted snacks. *Regul. Toxicol. Pharmacol.* **26,** 200–209.

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Final Report - Cohorts 1 through 6
Randomized, Double-Blind, Placebo Controlled Consumer Rechallenge Test of Olean Salted Snacks

Sponsor	The Procter & Gamble Company Winton Hill Technical Center 6071 Center Hill Avenue Cincinnati, OH 45224
Contract Research Organization	MarketVision, Inc. of Cincinnati, OH (Cohorts 1-4) Walker Clinical Evaluations (WCE), Indianapolis, IN (Cohorts 5-6)
Investigator	David Biederman (P&G employee) (Cohorts 1-4) Winston Satterlee, MD (WCE) (Cohorts 5-6)
Study Sites	Eau Claire, WI Cedar Rapids, IA Grand Junction, CO (Cohorts 1-2) Columbus, OH (Cohorts 3-4) Indianapolis, IN Bloomington, IN (Cohorts 5-6)
Sponsor's Study Personnel	Nora Zorich, MD, PhD Karen Riccardi Julie Kesler, BS, MBA
Study Number	Procter & Gamble Number FP144
Study Dates	August 5, 1996 to September 19, 1997 (Cohorts 1-6)

Regulatory Compliance and Quality Assurance

This study was conducted in compliance with Good Clinical Practices as proposed in the United States 21 Code of Federal Register 50, 52, and 56. Data contained in this report have been checked by Procter & Gamble, WCE Clinical Evaluations (WCE), Statking Consulting, Inc. and Market Vision Research, Inc., against original data sheets from the clinical site or sub-contractors.

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Appendices *

* Appendices were submitted directly to the FDA's Office of Premarket Approval and portions may be requested by way of the Freedom of Information Act.

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Final Report - Cohorts 1 through 6
Randomized, Double-Blind, Placebo-Controlled Consumer Rechallenge Test of Olean Salted Snacks

Summary

Consumers who spontaneously reported experiencing gastrointestinal symptoms after consuming Olean salted snacks and who agreed to participate, were enrolled in a 4-period, 2-treatment, within subject crossover study to compare the incidence of gastrointestinal symptoms between consumers eating chips made with Olean and those eating conventional full fat chips to address whether there would be more symptom reporting after eating chips made with olestra. Rechallenging this self-selected population, who believed they experienced gastrointestinal symptoms as a result of consuming Olean snacks, helps put the initial experience in perspective not only for the manufacturer but more importantly, for the consumer. This submission is the third and final report for this study describing the results for all 6 cohorts of participants (98 subjects). The first and second interim reports described the results from participants in cohorts 1, 2, 3, and 4.

Methods. After agreeing to participate and signing informed consent, each subject visited the study site four times and was provided two ounces of either potato chips containing olestra or conventional, full fat chips. All four products were different in appearance to maintain blinding. Consumption was monitored by direct observation and by weighing the test products pre- and any remaining product post- consumption. Participants were contacted three days after consuming the chips and questioned about whether they experienced gastrointestinal symptoms since eating the product that week. Subjects could also report, at any time, undesirable experiences to the study physician (cohorts 1-4) or the investigating physician (cohorts 5-6) via a toll-free 1-800 line.

Results and Discussion. For nearly three quarters of these participants, the amount of olestra consumed in the Rechallenge Study was comparable to, or greater than, the amount associated with their initial call. Of the 98 consumers who participated in the study, 88 (90%), had initially called to report that they had experienced diarrhea, and/or loose stool, and/or abdominal cramping. Upon rechallenge, there were no differences in the numbers of reports of gastrointestinal symptoms including abdominal cramping, diarrhea, and/or loose stool after eating Olean chips compared to after eating full fat chips. While 48% of these participants described the symptoms that prompted their initial call as severe, only four participants reported severe symptoms upon rechallenge (all four after consuming full fat chips) and the overall symptom severity ratings for all subjects were similar between the two treatments.

Conclusion. The results presented here are consistent with prior clinical experience with olestra and demonstrate that a two ounce serving of olestra is no more likely to result in reports of gastrointestinal symptoms including, diarrhea, loose stool or abdominal cramping than when consumers eat full fat snacks as a part of their usual diet. Further, these results suggest that initial calls to the 800-line may reflect false attribution of symptoms to products made with Olean. These findings support that a more informative label on products made with Olean, would be helpful for consumers by providing information about the context of consumption that is associated with an increased possibility of symptom occurrence. For example, this study, and the recently published Acute Consumption Study (a.k.a. Theater Test), demonstrates that single eating occasions of typical amounts of olestra savory snacks are not associated with increased GI symptoms.

FP-144
Final Report - Cohorts 1 through 6
Randomized, Double-Blind, Placebo Controlled Consumer Rechallenge
Test of Olean Salted Snacks

Introduction

Olestra (Olean brand, Procter & Gamble) is a non-absorbed fat replacer approved in January, 1996, by the FDA for use in savory snack foods (e.g. potato chips, corn chips, extruded snacks and crackers). Products made with Olean were initially marketed in three test cities by the Frito-Lay Company in April, 1996, under the Max brand name. The Olean products included both corn chip and potato chip snacks, regular and flavored. In September 1996, Procter & Gamble (P&G) began marketing Fat free Pringles in Columbus, Ohio. On February 24, 1997, Frito-Lay introduced the WOW! product line of potato and corn chips made with olestra in central Indiana while Fat free Pringles was introduced by P&G in Indiana in March, 1997. Also, during this period Nabisco introduced Fat free Wheat Thins and Fat free Ritz in Marion, Indiana.

All Frito-Lay Max, WOW!, Pringles Fat-Free Pringles and Nabisco fat-free crackers are labeled with the Olean ingredient trademark and also display the following information statement: "**This Product Contains Olestra.** Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added." The Frito-Lay Max and WOW! product labels refer consumers to a 1-800 telephone number staffed by the Frito-Lay Company. The Nabisco product labels refer consumers to a 1-800 telephone number staffed by the Nabisco Company. The Pringle Fat-Free product label refers consumers to a 1-800 telephone number direct to Procter & Gamble.

Post-marketing surveillance is conducted by Procter & Gamble for all spontaneous reports of symptom complaints alleged to be associated with the consumption of Olean containing products. Most reports are received through the 1-800 telephone number listed on the products. These calls are initially received at Frito-Lay Consumer Relations for their products, Nabisco Consumer Relations for their products and P&G Consumer Relations for Pringles. If symptoms are reported, calls that come to Frito-Lay or Nabisco are immediately transferred to Consumer Services at P&G for the call to be handled by P&G Consumer Relations. There is detailed data collection for all calls and, when indicated, follow-up by a health care professional. Reports also come into P&G directly through separate 1-800 numbers, by calling any of the P&G consumer lines, or through written correspondence. These consumers are queried about their interest in participating in a rechallenge study.

This report is a composite of all previously submitted interim reports (cohorts 1 to 4) along with the final two cohorts (5-6).

During the time period April 22, 1996 through June 5, 1997, a total of 1,134 reports of alleged possible adverse effects associated with Frito-Lay Olean products, Nabisco Fat-free products, and P&G Fat free Pringles were received from consumers; 640 from Frito-Lay consumers

through the Frito-Lay 1-800 number, 444 from Pringles consumers through the Pringles 1-800 number, one from Nabisco, and 49 who reported through general P&G 800-lines. These consumers comprise the population from which subjects were recruited for all six cohorts of the study.

The vast majority of these 1134 consumers were invited to participate in the study. Thirty four of these consumers were not eligible for participation as they did not meet the eligibility requirements of the study not having reported gastrointestinal symptoms when they initially called.

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Study Objective

The objective of this study, which was run under blinded conditions and standardized eating occasions, was to rechallenge consumers who believed they had experienced GI symptoms because they ate chips made with Olean. The information will provide a better understanding of the consumer's experience that initially prompted them to call P&G Consumer Relations, will help the consumer put their initial event into perspective and help address whether reports of diarrhea, loose stools and cramping are associated with Olean consumption or have been influenced by the information label, and/or negative publicity, or other uncontrolled factors experienced by the consumer.

Study Design and Rationale

Overall Study Design

The study is a double-blind, placebo-controlled, 4-period, 2-treatment within subject crossover design. The protocol was reviewed and approved by the Institutional Review Board of Procter & Gamble for cohorts 1 - 4, and by the Institutional Review Board of Walker Clinical Evaluations for cohorts 5 and 6. Subjects were recruited from all consumers who spontaneously reported an adverse gastrointestinal effect they associated with consumption of Olean-containing products directly to P&G Consumer Relations, or by call transfer from Frito-Lay. All subjects signed an informed consent prior to beginning the study procedures.

Study sites for cohorts 1 and 2 were located in the three test market cities (Eau Claire, Wisconsin; Cedar Rapids, Iowa; and Grand Junction, Colorado) where Frito-Lay Max brand salted snacks containing Olean were sold. Cohorts 3 and 4 were conducted at a single study site located in Columbus, Ohio, the test market for Fat free Pringles brand salted snacks. Cohorts 5 and 6 were conducted in Indianapolis and Bloomington, Indiana where Frito-Lay, Nabisco and P&G Olean products were available. Nabisco products were available in Marion, Indiana. These sites were selected as being convenient for the majority of potential subjects. Potential participants who reside outside these cities were offered the opportunity to participate with additional compensation for travel.

Each subject visited the study site four times at weekly intervals, and was provided two ounces of either potato chips containing Olean (two occasions) or conventional, full fat potato chips made with triglyceride (two occasions) that were randomly assigned to the four visits. Products were consumed at the site. At the first visit only, subjects were asked to provide information on their general medical history and medication use. At all visits, subjects were asked to list the foods they had consumed that day prior to their visit, and if they were currently experiencing any digestive symptoms prior to consuming products. This information is provided in the Study Case Report Forms in Appendix 2. Consumption was monitored by direct observation and by weighing the test product pre- and post-consumption. Subjects could remain at the site for up to two hours.

Three to five days following each test product consumption, subjects were contacted by telephone and asked if they had experienced any digestive effects during their participation in the study. If the subject answered "no", he/she was asked two product attribute questions in an effort to minimize subjects initially answering "no" to avoid answering further questions. If they answered "yes", information about their symptom(s) was recorded on Adverse Experience forms. Subjects who answered yes were further asked questions about food intolerances, medication use and illness among other household members. Any non-gastrointestinal symptoms volunteered were also recorded. All information was captured on study Case Report Forms provided in Appendix 2. The study physician for cohorts 1-4, Dr. Christopher Sweeney (a practicing

physician in Cincinnati, Ohio who consults for P&G but is not an employee), was also available to the subjects by telephone for the reporting of symptoms at any time. For cohorts 5-6, Winston Satterlee, MD, the study investigator for Walker Clinical Evaluations, was also available to the subjects at the site and by telephone at any time.

Treatment Assignment and Blind

Subjects received the two Olean and two placebo products in random order as determined by a balanced randomization scheme. To decrease the possibility of subjects breaking the blind due to product appearance or sensory attributes, two different Olean products and two different placebo products were used. The balanced randomization scheme is shown in Exhibit 1. One hundred-series numbers were assigned to participants in Eau Claire, WI, 200-series numbers to Cedar Rapids, IA, 300-series numbers to Grand Junction, CO, and 400-series numbers to participants at the Columbus, OH site. For Indianapolis and Bloomington, Indiana, series numbers 500 and 600 were assigned.

A schedule of study activities is shown in Table 1.

Table 1

Activity Schedule

	Visit 1		Visit 2		Visit 3		Visit 4	
	Site Visit	Phone Call	Site Visit	Phone Call	Site Visit	Phone Call	Site Visit	Phone Call
Informed Consent	X							
Medical History	X							
Medication Use	X							
Visit Questions*	X		X		X		X	
Chips Consumed	X		X		X		X	
Digestive Effect Questions		X		X		X		X

* Foods consumed prior to site visit; current digestive symptoms.

Study Sites and Investigator

For cohorts 1-4, the study was conducted by MarketVision, Inc. of Cincinnati, Ohio. The protocol was reviewed and approved by the Institutional Review Board of Procter & Gamble. The Investigator was David Biedermann, a P&G employee. The study physician was Christopher Sweeney, MD.

For cohorts 5-6, the study was conducted by Walker Clinical Evaluations of Indianapolis, Indiana. The protocol was reviewed and approved by WCE's Institutional Review Board. The investigator was Winston Satterlee, MD, who assumed investigator and study physician's responsibilities previously held by David Biedermann and Christopher Sweeney, MD.

Cohorts 1 and 2 were conducted at a single site in each of three cities, Eau Claire, Wisconsin; Cedar Rapids, Iowa; and Grand Junction, Colorado. Cohorts 3 and 4 were conducted at a single site in Columbus, Ohio. Cohorts 5 and 6 were conducted at two sites, Indianapolis and Bloomington, Indiana.

Curricula vitae of key study personnel are provided in Appendix 1.

Subject Selection

Subject Demographics

Participants of the study were recruited from the consumers who had spontaneously reported adverse product experiences, including gastrointestinal symptoms, which they associated with the consumption of products containing Olean brand fat replacer, to Consumer Relations, Procter & Gamble. This included 1,100 potential participants. Recruitment was not restricted to subjects in the test market cities, but also included consumers who lived out-of-state. Non-participating subjects included individuals who could not be contacted, individuals who refused participation, or individuals who could not fit study participation into their schedules.

Ninety-eight subjects completed the study; 11 subjects in the 1st cohort, six subjects in the 2nd cohort, 10 subjects in the 3rd cohort, and 30 in the 4th cohort, 19 in the fifth cohort, and 22 in the 6th cohort. The age and sex distribution of participating rechallenge subjects are compared to the total population of consumers who have called to report alleged adverse product experiences (shown in Exhibits 2 and 3).

Subjects Symptoms Reported During Original Phone Contact

Listings of symptoms which prompted study participant's initial call and the amount of olestra they described consuming are provided in Exhibits 4a through 4f for cohorts 1, 2, 3, 4, 5, and 6 respectively. Severity scoring for these symptoms as assigned by the consumers, when available, are noted as superscripts and defined in the Exhibit 4 footnotes. Forty-seven (48%) participants in the Rechallenge Study had initially reported "severe" symptoms when they called. This compares to 44% of the symptom reports from the total population of consumers who called. Additionally, 21% of participating subjects did not initially provide severity scores, compared to 29% of the total population.

Admission criteria

In order to qualify for admission, a subject had to:

1. For cohorts 1-4; those consumers who spontaneously contacted Consumer Relations, Procter & Gamble with a report of one or more gastrointestinal symptoms; persons appearing at the press conferences sponsored by CSPI in Columbus were personally asked if they would participate in the Rechallenge Study. For cohorts 5 and 6; the attempt to include these consumers was formalized so that any consumer appearing in print or at a press conference was contacted by Walker Clinical Investigations if their phone number could be identified.
2. Provide a signed informed consent statement, or if under the minimum legal age, be able to obtain written informed consent of a legally authorized representative.

Exclusion criteria

A potential subject was excluded if :

1. Another household member was currently participating in this study. (Additional interested household members were asked to participate in subsequent waves of the study).
2. There was a physical or mental condition present which, in the opinion of the investigator, would prevent the subject from completing the study procedures as specified in the protocol.

Subject Assignment and Identification

The subjects were randomly assigned to the treatment sequences using a balanced randomization scheme. Each subject was assigned a three-digit number that uniquely identified the subject when used in conjunction with the first four characters of the protocol number and the four digit investigator number. The three digit number also identified subjects with respect to site (first digit). For example:

FP144	-	1062	-	100
(Protocol)		(Investigator)		(Subject)

Treatment sequences were assigned by the project biostatistician to subject numbers. The subject numbers were assigned by each study site in the order that subjects enrolled in the study. Neither the study personnel, including the investigator, study monitor, data entry personnel, study physician, project physician and study site staff, nor the subjects, knew which subjects were assigned to which treatment sequence.

Rationale for Study Design

Test Product: Plain potato chips were selected as the best salted snack type to use in this study. Potato chips enjoy a high market penetration and are well accepted by consumers. Plain potato chips also offer the advantage of avoiding confounding factors such as gastrointestinal symptoms related to corn products or seasonings.

Serving Size: A two ounce serving of potato chips was selected as the appropriate amount to rechallenge consumers who had reported digestive effects when they previously consumed snacks containing Olean. Factors supporting this selection include:

- In over 60% of the reports of alleged adverse gastrointestinal effects, reported from April 22 to June 5, 1997, to Frito-Lay's consumer comment line or to the Pringles 800 line, consumers stated that they ate two ounces or less of Olean salted snacks. (P&G Quarterly reports for Olean submitted July 15, 1996, October 15, 1996, January 15, 1997, April 21, 1997, and July 22, 1997).

- The appropriateness of the serving size is supported by USDA data on salty snack consumption which show that two ounces exceeds the mean serving size for a single eating occasion consumption of potato chips for both males and females and all ages. (USDA) US /Department of Commerce (1986).

- A study by Dr. Barbara Rolls at Pennsylvania State University examined the acute potato chip eating behavior in 100 normal healthy lean and obese, male and female volunteers provided ad libitum access to chips as a snack. Approximately two ounces was the mean acute self-selected consumption in this group (1).

- The majority of calls to the 800-line numbers have reported stool changes and symptoms after consumption of chips in the 2 ounce range or less. This was unanticipated as the existing placebo-controlled data would predict that consumption of a single serving of 2 ounces of Olean chips would not be expected to result in alteration in stool character (2, 3, 4, 5, 6) and hence, potential symptoms. Testing in this range would allow for the identification of a uniquely sensitive population that had not been previously identified.

- In a recently completed study 1,136 participants, ranging in age from 13 to 88 years, were provided a 13 ounce bag of potato chips and told to eat as much as they wanted. The median consumption of Frito-Lay Max chips was 2.1 ounces. There was no dose-dependent relationship of olestra consumption and symptoms in this study. (7) (Study results presented to the Office of Scientific Support on 4/8/97, report submitted June 25, 1997).

Using a single standard of a reasonable serving size throughout the study for all subjects allows data to be compared across subjects, study sites and cohorts. On a practical level, the amount of chips served needed to be an amount that all participants, regardless of age, would be willing to eat on four occasions. Eating the products on two occasions provides information about whether symptoms reported by some consumers when eating products made with Olean are reproducible and, therefore, possibly related to consumption of Olean, per se.

Materials and Methods

Test Products

Product Form: The test products were plain potato chips prepared with Olean or conventional full fat chips made using triglyceride. Plain potato chips were chosen because they were available in the marketplace, they elicit good compliance, and they avoid the possible confounding factors presented by different types of corn chips or seasoned snacks.

For cohorts 1-4, Olean-containing chips were sold by Frito-Lay under the marketed name of Max products. The four specific products tested were: Frito-Lay Max, Ruffles (Olean), Frito-Lay Max Lay's (Olean), Frito-Lay Regular Ruffles (full fat/triglyceride) and Husman's Potato Chips (full fat/triglyceride).

For cohorts 5 and 6, the four specific products tested were: Frito-Lay WOW! Ruffles (Olean), Frito-Lay WOW! Lay's (Olean), Frito-Lay Regular Ruffles (full fat/triglyceride) and Husman's Potato Chips (full fat/triglyceride). Like all marketed Olean products, the Olean test product potato chips contained vitamins A, E, D, and K, at levels specified in the olestra approval regulations. These types were selected in order to minimize the potential for unblinding due to product sensory attributes.

Test product was purchased and repackaged in plain, food grade bags made of white foil laminate; one two-ounce bag for each of the four visits. Each bag was labeled with a declaration of contents, ingredient lists for both Olean and full fat triglyceride potato chips, a treatment code (cohorts 1-4, treatment codes were not placed on products for cohorts 5 and 6) and a statement that the contents were for research purposes only. Each bag bore the product information statement as specified earlier.

Administration of Test Product

Subjects were scheduled for individual site visits. Each test site was given detailed instructions on the administration of the potato chips to reduce variability between sites. Prior to serving, the potato chip bags were cut open neatly, poured into a bowl, and weighed. The bowl of potato chips was then placed on a tray with the empty bag displayed and a napkin, and served to the subject. Each subject was allowed to eat as much of the chips as they desired. If there were chips remaining, subjects were asked if they could eat more, but were not pressured to finish the entire serving. In addition, subjects were allowed to self-select a beverage from an assortment of regular cola, diet cola, regular lemon-lime soda, diet lemon-lime soda, or water. Subjects were allowed up to two hours in which to consume the potato chips. Subjects were asked to consume approximately the same amount of potato chips at each visit, and to choose the same beverage at each visit. The study visit was conducted in comfortable surroundings with television and magazines available. Consumption was discreetly observed by the interviewer.

Measurement of Test Product Consumption

The consumption of potato chips by each subject was determined by weighing the amount of potato chips before serving and the amount of chips remaining, if any, after consumption. The amount of Olean or triglyceride consumed was calculated from the weight of the chips consumed, using analytical data on the percent Olean and percent triglyceride in the chips.

Measurement of Gastrointestinal Experiences

For a majority of people, ingested food will transit the bowel within three days. Therefore, subjects were contacted by telephone three days (range 3-5 days) after each test product consumption visit to provide sufficient time for the subjects to experience an effect. Participants were told they will be called after three days and a time and number to contact them was agreed upon. Each subject was asked if they experienced any digestive changes since they ate the potato chips earlier in the week. If the subject responded "no", two product attribute questions about the acceptability of the taste and the product overall were asked. This was designed to avoid a skip bias, for subjects who might answer no to avoid answering more questions and minimize the call length. If the subject answered "yes", they were asked a series of questions to describe the symptom(s) experienced, time of onset, duration, date of cessation, and severity. For cohorts 1-4, subjects could report symptoms at the site or call the study physician at the toll-free phone number provided. Cohorts 5-6, the subjects could report symptoms at the study site, call the study site, or call the investigator physician at the toll-free number provided to them. In each instance, the same information was collected.

Subjects who reported GI symptoms were asked if any other member of their family or household had experienced symptoms similar to those reported, and if they had begun any new medications in the last week. This additional information was recorded on the Digestive Symptom/Phone Interview Form which is provided in Appendix 2, Case Report Forms.

Adverse Experience Reporting Procedures

For all six cohorts, subjects were provided 24-hour access for reporting adverse experiences to the study physician. Adverse experiences were collected via case report forms either during the site visit or during the Day-3 Telephone Interview. The majority of symptom reporting came from the Day-3 Telephone Interview.

Any symptoms or change in health reported by the subjects were recorded on case report forms. Adverse experiences reported by the subjects during the Day-3 Phone Interview were recorded directly on Adverse Experience case report forms. Completed Adverse Experience forms were forwarded to the physician for his review.

Other than the gastrointestinal experiences reported during the post-consumption survey, 12 subjects reported non-gastrointestinal adverse experiences. One subject in cohort 2 reported headaches, a pre-existing medical condition. Another subject in cohort 3 reported that she was 'dizzy' and 'shaky' 15 minutes after consuming test product. Symptoms resolved spontaneously.

In cohort 4, a 6 year old boy had a mild generalized rash. His mother called the boy's pediatrician and it was hypothesized that the rash was secondary to wearing a new sweat suit before it had been laundered. The rash resolved without treatment. Subjects 420 and 443 reported upper respiratory symptoms during the study. Subject 433 stated she was involved in an altercation and suffered traumatic injury to her mouth which caused her to withdraw from the study.

In cohort 5, subject 511, a 43 year old female, complained of knee pain during the second week of the study. Subject 517, a 27 year old female, complained of headaches during the study which was a preexisting condition. Subject 522, a 56 year old female, also complained of headaches during the study.

In cohort 6, Subject 602 was hospitalized with body aches, chills, fever and was diagnosed with "walking pneumonia" and urinary tract infection. The details of her clinical course can be found in the Individual Consumer Experiences section of this report. Subject 612, a 42 year old female with a history of asthma complained of shortness of breath, ankle swelling and an ear infection. Subject 623, a 16 year old female, entered the study with cold symptoms and was diagnosed during the first week of the study with an ear infection.

Adverse Experience Report Forms are provided in Appendix 2, Case Report Forms.

Statistical Methods

A sample size of 100 subjects, with 2 measurements per treatment per subject, has greater than 80% power to detect a 10% increase in incidence rates of gastrointestinal symptoms, using the assumptions that 1) the true placebo incidence rate is in the range of up to 15% and 2) the observations within individuals have little or no correlations. This sample size will yield even more power if the within-subject information is substantially correlated.

To compare the incidence of gastrointestinal symptoms between consumers eating chips made with Olean and conventional full fat chips, subjects were classified as to incidence of gastrointestinal symptoms (yes/no). Logistic regression analyses were performed to compare incidence of gastrointestinal symptoms between the two treatment groups. As this was a crossover (4 period, 2 treatment study), the logistic regression model was stratified (by subject) and included terms for visit effects and treatment effects (8, similar to Example 5.4 in this reference).

An exact conditional logistic regression analysis was performed using the LogXact software (9). Treatment groups were compared with respect to incidence of each of the following GI events:

1) any GI symptom
2) abdominal cramping
3) diarrhea
4) loose stools
5) diarrhea or loose stools
6) gas (eructation, flatulence, bloating)

Treatment groups were declared to be statistically significantly different if the one-sided (Olean > full fat) p-value was ≤ 0.05. No adjustments were made to the p-values even though there were multiple tests with respect to various GI symptoms.

Results - Cohorts 1 through 6

Subject Compliance

Of 98 subjects in the study, 92 completed all four weeks of the study. Two subjects dropped after the 1st visit, Subject 403, cohort 3, reported at the phone interview that "she didn't realize that she was going to have to eat that much" and "doesn't want to take the chance of getting sick." During the only visit she completed she consumed the two ounce serving of chips made with Olean. She did not report any symptoms prior to withdrawing from the study. Subject 432, cohort 4, called after the first visit to say that she did not want to continue in the study because she felt "uncomfortable" with participating. At the one visit she did complete, she consumed full fat chips and experienced stomach rumbling, urgency and loose stool as soon as she got home from the study site.

Subject 433 in cohort 4 completed two weeks of the study, though she was not compliant with consumption, eating less than one ounce at each visit. After the second visit she was involved in a "fight" in which she received an injury to her oral mucosa which limited her ability to eat potato chips, so she withdrew. She reported no symptoms after eating full fat chips and had mild cramping and diarrhea after eating Olean chips. Subject 623, a 16 year old also only completed two weeks of the study. She did not report experiencing any gastrointestinal symptoms after the two visits when she ate Husman's full fat and Ruffles WOW!, but was treated for an ear infection during the second week of the study. She was withdrawn when she failed to attend her scheduled visits.

Subject 450, cohort 4, was compliant, (at least two ounces of full fat and two ounces of Olean chips), but was unable to complete a fourth visit. He reported no gastrointestinal symptoms during the study.

Subject 601 withdrew from the study after completing three visits. She reported no symptoms after visit 1 when she ate Lay's WOW! chips or after Visit 2 when she ate Husman's full fat chips. After the third visit (full fat chips) she experienced diarrhea and abdominal cramping which worsened over the next few days to the point that she eventually required hospitalization. The details of her clinical course can be found in the Individual Consumer Experiences section of this report. As she consumed all product for three of the four visits she met the protocol-specified conditions for overall compliance (at least two ounces of full fat and two ounces of Olean chips) but not weekly compliance.

Compliance with potato chips consumption was very good with all but 10 participants meeting the protocol-specified criteria that at least one ounce of chips be consumed at each visit. Four of these participants with poor compliance withdrew as noted above. Overall compliance for each treatment is provided in Table 2. There were no meaningful differences between full fat and Olean chips.

Table 2

Compliance with Chip Consumption

% of two, 2 ounce servings consumed for each treatment	No. of Subjects (%) (n=98) Full Fat	Olean
< 50%	7 (7%)*	9 (9%)*
50 to 75%	25 (26%)	21 (21%)
76 to 89%	15 (15%)	20 (20%)
> 90%	51 (52%)	48 (49%)

* Subjects 403, 432, 433, 450, & 623 withdrew from the study. Subject 601 was withdrawn from the study after three weeks due to hospitalization. Subjects 446, 510, 515, 523, 609 and 615 completed the study but ate <50% at some or all of their visits.

Protocol Deviations

Protocol deviations were minor and judged not to affect the outcome of the study. All deviations are noted below:

Two subjects, 300 in cohort 1, and 522 in cohort 5, consumed a test product out-of-order compared to the balanced randomization guide. In both cases, this was a result of the research organization executing the study inadvertently bringing product to the study site out of sequence, so a substitution was made on site. The sponsor was notified, each time, and agreed that the subject's treatment assignment would be altered to change of order of product consumption. The blind was maintained for both subjects.

One subject, 615 in cohort 6, inadvertently received the same test product twice (i.e., treatment sequence was 2214 instead of 2413). The sponsor was notified and the person responsible for clinical product pack-out changed the product sequence to assure that the subject received full fat chips on two occasions and Olean chips on two occasions.

Four (439, 512, 521 and 614) subjects enrolled into the study without meeting the protocol entrance criteria. Subject 439, enrolled in cohort 4, phoned the 800 line to allege symptoms due to eating Olean chips. It was realized after the fourth cohort of the study was completed that she was not calling about herself but rather her seven year old step-son who lives in Virginia. When she was contacted (her name and phone number being listed on the post-marketing summary case report form), she agreed to participate. She was, in fact, enrolled in the study and completed all four visits with good compliance and without symptoms after any of the four visits.

Subject number 512, 521 and 614 enrolled into cohorts 5 and 6 of the study without reporting, to the 800 line, gastrointestinal symptoms; only consumers who voluntarily reported

gastrointestinal symptoms were eligible for the study. For cohorts 5-6, a list of consumers who called P&G's Consumers Relation's Department was given to WCE for recruiting purposes. This list consisted of consumers who reported gastrointestinal symptoms, as well as non-gastrointestinal symptoms. The list did not contain the consumer's original adverse event, therefore, WCE attempted to recruit all consumers. Consequently, subject number 512 who initially reported hives, and subject number 521 and 614 who initially reported a rash where enrolled in cohorts 5 (512 and 521) and 6 (614). None of the subjects had any rashes the weeks after eating Olean chips. Subject 614 had mild diarrhea after one eating occasion of triglyceride chips. Since these subjects did not meet the protocol inclusion criteria of having contacted P&G alleging experiencing gastrointestinal symptoms after eating snacks made with olestra, they were not included in the analyses or in any of the tabular summaries. Had these additional four subjects been eligible, they would have increased the final completed count to 102.

Twenty of the 379 total contacts (5%) were outside the protocol specified window of 3 to 5 days after product consumption; five were contacted early (after two days) and fifteen were contacted after the 5 day window (six on day six, five on day seven, two on day eight, one on day 10 and one not until 16 days after product consumption). The early phone contacts were made at the subjects' request. In all cases where the subject was contacted after the five day window, attempts were made within the window, with protocol noncompliance reflecting issues of participants' availability by phone even though a specified time to contact was pre-established by the participants prior to leaving the study site.

Incidence of Gastrointestinal Symptoms

The occurrence of specific gastrointestinal symptoms by visit is shown in Exhibits 5 through 10 for all subjects for Any GI Symptom, Abdominal Cramping, Diarrhea, Loose Stools, Diarrhea or Loose Stools, and Gas, respectively. For each visit after which a subject reported the particular symptom indicated in the table, the visit has been marked by shading. The abbreviations F1 and F2 refer to the two different types of full fat chips that were consumed. The abbreviations O1 and O2 refer to the two different types of Olean chips that were consumed. No significant period effect on symptom reporting was observed for any symptom for any period in the study.

As shown in Exhibits 5 through 10 and summarized in Table 3, thirty of the ninety eight subjects reported no symptoms during the study, twenty one subjects reported symptoms one time in the week after eating Olean chips, twenty subjects reported symptoms one time in the week after eating full fat chips, four subjects reported symptoms both times they ate full fat chips but not after eating Olean, five subjects reported symptoms both times they ate Olean but not after eating full fat chips, eleven subjects reported symptoms once after full fat chips and once after eating Olean chips, two subjects reported symptoms both times they ate full fat chips and once when they ate Olean chips four subjects reported symptoms both times they ate Olean chips and once when they ate full fat chips, and one subject reported gastrointestinal symptoms after all four

weeks of the study. These data are combined in Table 3 to look at frequency of symptoms reported after each of the 109 eating occasions of full fat or the 110 eating occasions of Olean chips (94 people, eating each type of chip 2 times, one person eating Olean chips once, one person eating full fat once, one person eating Olean chips once and full fat once, and one person eating Olean chips twice and full fat chips once).

Table 3

Occurrence of Gastrointestinal Symptoms after Consumption of Olean and Triglyceride

Occurrence of Gastrointestinal Symptoms	Number (%) of Participants (n=98)
No symptoms reported during the study	30 (31)
Symptoms reported after one eating occasion	
After one Olean eating occasion	21 (21)
After one triglyceride eating occasion	20 (20)
Symptoms reported after two eating occasions	
After both Olean eating occasions	5 (5)
After both triglyceride eating occasions	4 (4)
After one Olean eating occasion and one triglyceride eating occasion	11 (11)
Symptoms reported after three eating occasions	
After both Olean eating occasions and one triglyceride eating occasion	4 (4)
After both triglyceride eating occasions and one Olean eating occasion	2 (2)
Symptoms reported after all four eating occasions	1 (1)

Table 4

Incidence of GI Events by Treatment

	Full Fat	Olean
Any GI Symptoms	26%	28%
Cramping	9%	12%
Diarrhea	8%	6%
Loose Stools	7%	5%
Diarrhea or Loose Stools	15%	11%
Gas (eructation, flatulence, bloating)	5%	7%

A graphical summary of the data from Exhibits 5 through 10 is shown in Exhibit 11. As seen in Table 3 and Exhibit 11, there was comparable reporting of any GI symptom, cramping, and loose stool, with these symptoms being reported with similar frequency after either Olean or regular triglyceride chip consumption. There was a numeric increase in reports of cramping with Olean consumption (12% vs. 9%) and numeric increases in reports of diarrhea (8% vs. 6%) and diarrhea or loose stools with full fat chips consumption (15% vs. 11%). Individual subject experiences while participating in this four period cross-over study are provided in Exhibits 12a through 12f for cohorts 1-6, respectively.

Gastrointestinal Symptoms - Individual Consumer Experiences by Cohort

To provide a more complete perspective on the individual consumer's experience and for the convenience of the reader, narratives are provided that summarize the consumer's initial call, their experiences during study participation, and any other relevant medical or dietary history. Details of the initial call are excerpted from the Summary Case Reports as submitted in Quarterly Post-Marketing Surveillance Summary Reports are submitted to the Office of Scientific Support, Food and Drug Administration, Center for Food Safety and Nutrition. To facilitate comparing the individual subject's study experience with their initial report to P&G, a copy of the Post-Marketing Surveillance Summary Report is included along with the Case Report Forms in Appendix 2. A listing of subject study numbers and P&G's Post-Marketing Surveillance identification numbers (ALERT numbers) are provided in Exhibit 13.

Cohort 1

When repeatedly rechallenged, five subjects reported symptoms only one time during the four weeks of study.

Subject 100, a 46 year old male, initially reported cramping and loose stools three hours after eating eight chips. During the study, he reported a mild upset stomach 10 hours after eating Olean chips one time.

Subject 202, a 37 year old female, initially reported belching, an upset stomach and gas thirty minutes after eating three to four servings of chips. During the study, she had mild burping one time one hour after eating Olean chips.

Subject 204, a 33 year old male, initially reported diarrhea twenty-four hours after eating nacho cheese, barbecue and regular chips, which he estimated 12 ounces total over the weekend. He did not have symptoms when he ate Olean chips but reported mild cramping and loose stools one time after eating regular chips.

Subject 300, a 41 year old female, initially reported diarrhea and abdominal pain in the morning after eating six handfuls of chips over the course of the previous evening and the next morning. During the study she reported moderate gas, bloating, "diarrhea/loose stools" eight hours after eating Olean, on one occasion. (She did not separately describe episodes of diarrhea and loose stool but used the combination of terms to describe her symptoms).

Subject 301, a 59 year old female, initially reported gas, bloating, and loose stool about ten hours after eating seven to eight handfuls of chips. She stated that she had eaten chips over several occasions and always had the same symptoms. During the study, she reported mild flatulence, bloating, and burping two hours after eating Olean chips and stated she had diarrhea two days later. This was reported after eating Olean chips one time, but not the other.

Three subjects had symptoms on more than one occasion.

Subject 101, is a 16 year old female whose father initially reported that she experienced severe abdominal cramping and diarrhea 12 hours after eating chips on two occasions, the first after eating a sample bag (3/4 ounce) and 10 to 12 chips at another occasion. During the study, she had no symptoms to report after eating Olean but described moderate cramping two days after eating full fat chips on one occasion and moderate cramping and diarrhea two days after eating full fat chips the second time.

Subject 200, a 58 year old female, initially called to report moderate cramping and diarrhea three hours after eating two handfuls of chips. During the study, she reported moderate flatulence two hours after eating Olean chips on one occasion and although she didn't have any other problems she took Imodium "just in case", because she was "having company that night". She reported moderate cramping and an upset stomach two hours after eating Olean chips the second time. Daily diet records were obtained on test days during the rechallenge study. It is of interest that this subject appeared to regularly consume dietetic jam in the morning that most likely would contain sorbitol. She also took FiberCon on a regular basis.

Subject 201, a 51 year old female, initially called to report abdominal cramping one hour after eating about one ounce of chips three days in a row. During the study, she reported gas pains and abdominal cramping that brought on a "need to use the rest room" five hours after eating Olean on one occasion and cramping and flatulence two hours after eating Olean chips the second time. She stated that her normal activities were not impaired by these symptoms.

The remaining three subjects did not report any symptoms at any point during the study.

They were **subject 102**, a 39 year old female, who initially described moderate abdominal cramping sixteen hours after eating four to five ounces of chips; **Subject 203**, a 27 year old male who initially described diarrhea, cramping and urgency two to three hours after eating about two ounces of chips; and **Subject 302**, a 72 year old man who had initially reported diarrhea 10 to 12 hours after eating a few handfuls of chips.

Cohort 2

Four subjects in Cohort 2 reported symptoms only after one eating occasion.

Subject 120, a 50 year old female, first called after eating one-half of a sample bag on two different occasions (approximately 3.8 g/olestra each occasion, about 1/2 ounce of chips). She reported that 17 hours after eating the chips she experienced cramping and diarrhea. The symptoms occurred both times she ate product and were described as worse the second time. Symptoms lasted 30 to 45 minutes both times. During the study, she described stomach cramping and diarrhea, rated as moderate, four days after eating full fat chips on one occasion. Also she described intermittent headaches during the study which she stated preceded study participation. No other symptoms were reported related to the three subsequent chip-eating occasions.

Subject 121, a 49 year old female with a history of diabetes mellitus requiring insulin, first called to report that she experienced moderate abdominal cramping five minutes after eating two ounces of chips. Symptoms lasted "about half an hour". During the study, she described mild stomach cramping that started 20 minutes after eating Olean chips and lasted thirty minutes and was accompanied by mild diarrhea which started 90 minutes after eating the chips and lasted 12 hours. She self-medicated with Pepto-Bismol. Symptoms were experienced only after one eating occasion.

Subject 221, a 42 year old female, first called to report that after eating ten chips a day for seven consecutive days she experienced loose stools, rectal burning and gas after the first five days which stopped when she stopped eating the chips. During the study, she reported moderate cramping that began fourteen hours after eating full fat chips on one occasion. She reported no other symptoms during the remainder of the study.

Subject 320, a 67 year old female, first called to report that she experienced upper abdominal pain and gas one hour after eating a sample bag of chips (6 gram of olestra, just under an ounce of chips). The symptoms lasted for four hours. She volunteered that she experiences similar symptoms when she drinks soft drinks. During the study, she reported one episode of mild diarrhea one hour after eating full fat chips on one occasion during the study. No other symptoms were reported for the other three treatment periods.

Two participants reported no symptoms during their participation in the study.

Subject 220, a 50 year male with a history of obesity and hypertension on doxazosin (Cardura) and diabetes for which he takes glyburide (Glynase) and insulin, first called to report that everyone in their family of four experienced cramping and diarrhea about five hours after each eating two ounces of chips. Symptoms lasted for eight hours. The subject stated that he had similar symptoms when he would eat sugar-free candies. This subject reported no symptoms during participation in this study.

Subject 321, a 72 year old female with a history of hypertension currently treated with hydrochlorothiazide, first called to report that she ate five or six chips and had nausea but the week prior to that she had cramping and diarrhea 45 minutes after eating 25 Olean chips (12.5 grams of olestra about one and a half ounces of chips) on two different occasions about four days apart. Each time she had a single bowel movement about one and a half hours after eating the chips. During the study she reported no symptoms on any eating occasion.

Cohort 3

In this Cohort three participants reported symptoms after one eating occasion only.

Subject 401, a 38 year old female with a history of hypothyroidism for which she takes levothyroxine, and surgical menopause for which she takes conjugated estrogens, first called to report that she experienced moderate abdominal cramping, and three days of diarrhea and urgency, the day after eating eight potato chips. During this study, she reported cramping and urgency fourteen hours after eating Olean chips on one occasion. Symptoms were rated as mild and resolved without intervention.

Subject 405, a 47 year old female with a history of thyroid disease, depression and dyspepsia taking levothyroxine, paroxetine, and ranitidine, first called to report that she experienced cramping and severe diarrhea 12 hours after eating a total of five ounces of Olean chips. She had also eaten one ounce of chips on the previous day. The symptoms lasted for two and a half days and she took Kaopectate. When contacted to participate in the study, she volunteered that four of her friends became ill with diarrhea and cramping within two weeks of her symptoms (none of her friends having eaten olestra). During the study she experienced symptoms on one occasion. She reported "diarrhea" (one bowel movement) and abdominal cramping one day after eating full fat chips. No other symptoms were reported at any time.

Subject 409, a 26 year old female, first called to report that she experienced dizziness, shakes, and tunnel vision 20 minutes after eating a sample of Pringles she received. The symptoms lasted one day. During the study she reported symptoms once. Fifteen minutes after eating olestra on the second occasion she felt shaky and dizzy. These symptoms lasted for two hours. In addition she reported mild abdominal cramping that began one hour after consumption (thirty minutes after the other symptoms) which lasted for 45 minutes. No other symptoms were reported.

Four participants reported symptoms twice.

Subject 400, a 28 year old female, with a history of obesity for which she takes fenfluramine and phentermine, and herpes simplex for which she takes acyclovir, first called to report four days of loose stool that was oily and orange in color after eating one can of Pringles over the course of three days. Symptoms abated without intervention. She also describes intolerance to milk products with "gas and diarrhea" and selects a variety of reduced fat and calorie foods. During the study, she reported symptoms after two eating occasions; once after eating full fat and once after eating Olean chips. The day after eating full fat chips on one occasion she reported mild loose stools that lasted for four days. Ten hours after eating Olean chips on one occasion she reported 15 minutes of moderate abdominal cramping. No medication was taken for these symptoms and she reported no symptoms on the other two eating occasions.

Subject 402, a 30 year old male with a history of heartburn for which he takes cimetidine, first called to report that he experienced moderate loose green stools with gas and headache after eating a total of seven Olean chips over three days (total exposure 3.5 grams or about a half ounce of chips). Similar symptoms occur after he eats at "Taco Bell" or drinks beer. He told this to his physician during a routine visit and was told to stop eating the chips. During the study this subject reported symptoms after eating Olean chips on both occasions. On the first eating occasion he reported increased stool frequency that started 12 hours after consumption and lasted two days. Twelve hours after the second eating occasion he reported increased number of bowel movements that were loose. Symptoms resolved after 36 hours without intervention. No other symptoms were reported.

Subject 407, a 22 year old female with a history of asthma, first called to report that she experienced five hours of moderate abdominal cramping 30 minutes after eating eight Pringles chips (4 grams of olestra). She volunteered that she has similar symptoms after eating at "McDonald's". During the study, she reported symptoms both times after eating full fat chips but never after eating Olean chips. Both times she described stomach cramping 30 minutes after eating the full fat chips. Symptoms resolved within an hour. She reports taking Tums.

Subject 408, a 40 year old female, first called to report having moderate diarrhea about three hours after eating 15 Pringles chips (7.5 grams of olestra). Symptoms resolved within three hours. During the study she reported having gas 11 hours after eating Olean chips on one occasion and 12 hours after eating full fat chips on one occasion. No other symptoms were reported.

One participant reported symptoms after three eating occasions.

Subject 406, a 44 year old female, on no medications, first called to report that she experienced moderate loose stools, diarrhea and cramping after eating a total of 18 chips (9 grams of olestra) over two days. She described at that time that she eats a very high fiber diet and frequently has symptoms of this nature after eating bran, prunes, herbal tea, rye bread and beans. During the study, she described gastrointestinal symptoms after three eating occasions; twice after eating full fat chips and once after eating Olean chips. Sixteen hours after eating full fat chips the first

time she described having soft stool that lasted for one day. Two days after eating Olean chips on one occasion she described mild cramping that lasted for one hour. Fifteen hours after she ate full fat chips for the second time, she reported a single loose bowel movement that she rated as moderate. No treatment was taken for any of these symptoms.

Two participants reported no symptoms during the study.

Subject 403, a 73 year-old female with a history of glaucoma, first called to report that she experienced diarrhea, cramping, bloating, nausea and headache within hours of eating approximately twenty Fat free Pringles. She reported taking Imodium (loperamide) for the symptoms. During the study she ate two ounces of chips and reported experiencing no symptoms but decided to drop from the study after the first week because she thought it was too much to have to eat and she was concerned it might make her sick. The chips she ate during the first study visit were made with Olean.

Subject 404, a 47 year old female, first called to report experiencing severe diarrhea and cramping after eating a total of 36 chips (18 grams total, over two ounces of chips) over a period of seven days. Symptoms lasted for five days with a maximum of six watery bowel movements for which she took Imodium. During this study this subject reported no symptoms after any of the four eating occasions.

Cohort 4

In this cohort, 14 subjects reported symptoms after one eating occasion only.

Subject 420 is a 65 year old man with a history of hypertension and atherosclerosis who initially called complaining of cramping, diarrhea, and urgency within 30 minutes of eating 12 Fat free Pringles Crisps, lasting 45 minutes. He had eaten Fat free Pringles the week prior to this event without symptoms. During the study he reported symptoms of upset stomach, and symptoms of an upper respiratory tract infection three days after the third consumption period when he ate Lay's Max chips. He took Dimetapp and Tylenol for these symptoms. The symptoms lasted for 10 days. He did not have symptoms after any other visit.

Subject 421 is a 6 year old boy who, according to his mother, ate "a lot" of a sample can of Fat-free Pringles and had diarrhea two days later which lasted for two days. Four days after visit 2 when he consumed Olean chips, his mother called Dr. Sweeney to report that he had a mild generalized rash. His mother called the boy's pediatrician and it was hypothesized that the rash was secondary to wearing a new sweat suit before it had been laundered. After the third visit when he consumed full fat chips, he reported mild gas one hour after eating the chips and one episode of loose stools two days later. During this study he was only able to eat between 50% and 75% of the product at each of the four visits.

Subject 424 is a 38 year old female with a history of migraine headaches who initially called to report experiencing mild cramping and bloating four hours after eating a total of 12 Fat-free Pringles crisps. The symptoms resolved within six hours. She reported having eaten about 12

crisps the previous day also. During the study, two days after visit 1 when she ate Ruffles Max chips, she experienced a mild sensation of air bubbles in her stomach and mild bloating which lasted for one day. She reported no other symptoms following the next three visits. It is of note that this consumer reports that she has bloating and diarrhea after eating any fresh fruit or vegetables.

Subject 426 is a 20 year old male with a history of migraine headaches who appears to adhere to a low-fat diet. On the days we collected diet data he reported consuming fat-free cheeses and fat-free cooking sprays, plain bagels, pizza without cheese, and strips of chicken in a pita without cheese. He initially called to report that he experienced a stomach ache after eating three ounces of Fat free Pringles. The following day he ate another three ounces and had an upset stomach and diarrhea. During the study he only reported symptoms on one occasion. At visit 3 he had a mild stomach ache about three hours after eating Husman's full fat chips.

Subject 429 is a healthy 26 year old male who initially called to report that he experienced diarrhea and cramping within six hours of eating four ounces of Fat free Pringles. During the study he reported symptoms only after visit 1 when he described mild urgency and a single loose stool, 45 minutes after eating Lay Max chips.

Subject 432 is 38 year old healthy female who initially called to report experiencing cramping and diarrhea within fifteen minutes of eating three ounces of Fat free Pringles. She withdrew from the study after only one visit reporting loose stool, urgency, and stomach rumbling, fifty minutes after Husman's full fat chips. Her stated reason from withdrawing from the study was is "she was overall not comfortable with the study" and she specifically stated "she was concerned that she had a bowel movement immediately after returning home from the site and it was just too far to drive."

Subject 433 is a 33 year old female with a history of migraine headaches currently taking Valium for "nerves". She initially called to report that she experienced sharp pains in her lower abdomen and bloody diarrhea six hours after eating ten Fat free Pringles crisps. She reported that she went to see her primary care physician who referred her to a surgeon. In follow-up she stated that her symptoms had resolved and she decided not to go to the surgeon (presumably for a sigmoidoscopy). During the study she described severe cramping three hours after eating the chips at visit 2 and diarrhea 10 hours after chips which were Husman's full fat chips. This subject did not report any symptoms after visit 1 when she ate about half an ounce of Ruffles Max chips. This subject did not participate beyond the second visit. She related that during the third week of the study, she experienced a traumatic injury to her mouth and could not eat the chips. She was told to treat this injury with a mouthrinse (unspecified) and was given a tetanus shot.

Subject 435 is a healthy 17 year old female who initially called to report experiencing abdominal cramping within 12 hours of eating five Fat free Pringles. During the study she reported symptoms only one time which was after visit 1 when she reported experiencing mild abdominal cramping, gurgling in her stomach, and a headache eight to 17 hours after eating Lay's Max chips.

Subject 440 is a 47 year old female with a past medical history of hysterectomy, bladder surgery, and carpal tunnel syndrome currently hormone replacement therapy and a "pill for bladder control" who initially called to report that she experienced severe diarrhea within 24 hours of eating a total of three ounces of Fat free Pringles and again after eating "a few" Pringles. During the study she reported symptoms only after visit 1, describing severe diarrhea two days after eating Ruffles full fat chips.

Subject 442 is a 55 year old obese female who is currently participating in the Women's Health Initiative, taking hormone replacement therapy, aspirin and vitamin E, also taking theophylline for asthma who initially called to report experiencing severe diarrhea within four hours of eating a total of three ounces of Fat free Pringles. During the study she reported symptoms after only one visit. She reported mild abdominal cramping eight hours after eating Ruffles Max chips.

Subject 446 is a 40 year old healthy female who initially called to report experiencing mild abdominal cramping six hours after eating 10 Fat free Pringles. During the study she was not compliant with our request to have each participant eat at least one ounce. She ate less than 50% of the chips at each of the four visits. She reported symptoms after one visit only. Two days after visit 3 when she ate Ruffles Max chips she reported mild abdominal cramping that lasted for about 30 minutes.

Subject 447 is a 40 year old obese female who initially called to report experiencing severe diarrhea, cramping, and gas within 10 minutes of consuming six Fat-free Pringle chips. During the study she reported symptoms after only one visit. After visit 3 when she ate Ruffles Max chips, she reported mild cramping one hour later and mild diarrhea 13 hours later.

Subject 448 is a 49 year old female on medications for hypertension and depression who initially called to report experiencing severe cramping and diarrhea within 12 hours of eating four ounces of Fat free Pringles. During the study she reported symptoms after one visit only. Three to four hours after visit 3 when she ate Ruffles full fat chips she had moderate diarrhea for which she took Pepto Bismol.

Subject 449 is a 33 year old female taking multiple medications for asthma who initially called to report experiencing severe diarrhea and moderate abdominal cramping within 12 hours of eating 12 Fat free Pringles chips. During the study she reported symptoms after one visit only. Sixteen hours after visit 1 when she ate Husman's full fat chips she reported mild loose stools. She consumed between 50% and 75% of the chips at each of the four visits.

Four participants reported experiencing symptoms twice.

Subject 428 is a 65 year old female with a history of bilateral hip replacement, hysterectomy and arthritis taking estrogen and Relafen, initially called to report that she experienced severe abdominal cramping one hour after eating an entire can of Fat free Pringles. The symptom resolved within five hours without any treatment. During the study she reported symptoms after visit 1 and visit 4. She reported moderate nausea with five minutes and loose stools three hours after eating Husman's full fat chips. She also described mild nausea five minutes after eating Ruffles Max chips after visit 4 which lasted for 15 minutes.

Subject 436 is a 24 year old healthy female whose husband initially called to report that she experienced a headache and moderate loose stools after eating a total of 21 Fat free Pringles chips over three days. During the study she reported symptoms on two occasions, visit 2 and visit 4. She reported mild abdominal cramping and moderate loose stools, thirteen hours after eating Lay's Max chips. After visit 4 when she ate Ruffles full fat chips, she described moderate nausea and vomiting 13 hours later.

Subject 443 is a 27 year old healthy female who initially called to report severe abdominal cramping after eating 25 Fat free Pringles chips. During the study she reported symptoms after two visits. She reported feeling "queasy" 13 hours after eating Lay's Max chips at visit 1. The symptom was rated as mild and lasted 10 minutes. She also reported mild diarrhea and stomachache two days after visit 3 when she ate Husman's full fat chips. This subject also reported moderate headache, sore throat, rhinitis, chills and cough on the day of the last visit before product was consumed. She took Alka Seltzer Cold Formula.

Subject 445 is a 26 year old female with a history of hypercholesterolemia on no treatment who initially called to report moderate diarrhea, gas and bloating and moderate cramping within six hours of eating eight Fat free Pringles. During the study she reported symptoms after two visits. After visit 2 when she ate Ruffles Max, she reported moderate gas and softer bowel movements which she rated as mild. She also reported constipation 12 hours after visit 4 when she ate Lay's Max chips.

Three participants reported symptoms after three eating occasions.

Subject 430 is a 30 year old healthy male who initially called to report that he experienced severe diarrhea within six hours of eating 17 Fat free Pringles chips. During the study, he reported symptoms on three occasions. Sixteen hours after eating Ruffles full fat chips he reported mild urgency and a loose stool. He described mild abdominal cramping and mild loose stools 24 hours after visit 2 when he ate Lay's Max chips and mild loose stools 12 hours after eating Ruffles Max chips at visit 3.

Subject 431 is a 28 year old healthy male who initially called to report experiencing diarrhea (two loose bowel movements) within 12 hours of eating three ounces of Fat free Pringles which he described as similar to when he eats Indian and Curry foods. During the study he described experiencing symptoms after three visits. He described having "mushy" bowel movements and gas two days after eating Ruffles Max chips. Twenty four hours after visit 3 when he ate Husman's full fat chips he reported mild gas that lasted for 36 hours. He also described mild gas 24 hours after eating Lay's Max chips at visit 4.

Subject 434 is a healthy 40 year old female who initially called to report that she had an upset stomach with cramping six hours after eating two ounces of Fat free Pringles Crisps. She also described experiencing diarrhea 12 hours after eating the product. At that time all symptoms were rated as moderate. During the study, she reported having symptoms after three visits. After visit 1, she reported mild loose stool that occurred 12 hours after eating Ruffles full fat chips.

After visit 3, she again reported mild loose stools, 24 hours after eating Ruffles Max chips. After visit 4, she reported mild cramping eight hours and moderate diarrhea 12 hours after eating Husman's full fat chips.

Nine participants did not report gastrointestinal symptoms during the study.

Subject 423 is a 74 year old woman with a history of breast cancer who takes Motrin for arthritis and hydrochlorothiazide and potassium for "water retention". The initial call to P&G alleging an adverse event was made by her daughter who called to report that her mother experienced cramping and diarrhea within three hours of eating 10 to 12 Pringles chips (approximately 6 grams of olestra, under one ounce of chips). Her symptoms resolved within six hours. During her participation in the rechallenge study she reported no symptoms after any of the four consumption periods.

Subject 425 is a 72 year old man with a history of multiple bypass surgeries taking Isorbid, atenolol, Zocor, Norvasc and aspirin daily who initially called to report the he experienced mild diarrhea within 18 hours of eating one and a half ounces of Fat free Pringles. Symptoms resolved within one day. He also described noting a terrible aftertaste that persisted for 12 days. During the study he reported no symptoms after any of the four consumption periods. He consumed between 50% and 75% of the crisps at each one of the four consumption periods.

Subject 427 is a 62 year old male with no concurrent medical conditions taking only multivitamins, initially called to report that he experienced loose stools after eating three cans of Fat free Pringles over the weekend. He reported no symptoms after any of the visits.

Subject 437 is a 35 year old female taking oral contraceptives who initially called to report experiencing severe diarrhea within four days of eating two ounces of Fat free Pringles chips. From this subject's study diet diary it is evident that she consumes a variety of reduced fat products. She did not report any symptoms during the four weeks of the study. She consumed between 50% and 75% of the chips at each one of the four visits.

Subject 438 is an obese 35 year old female on no medications. She initially called to report that she experienced moderate stomach pain, mild diarrhea, and severe nausea three hours after eating 15 Fat free Pringles. She also reported that she had eaten two chips three and four days prior to these events. She reported no GI symptoms during the four weeks of the study.

Subject 441 is a 56 year old female on hormone replacement therapy who initially called to report experiencing severe abdominal cramping, severe gas, and moderate diarrhea two hours after eating one and one-half ounces of Fat free Pringles. During the study, she reported no symptoms with consumption between 50 % and 75% of product each of the four weeks. She rated the products as good to very good but did not choose to eat more.

Subject 444 is a 21 year old female with a history of asthma taking Ventolin and oral contraceptives who initially called to report experiencing severe vomiting and moderate diarrhea 12 hours after eating 10 Fat free Pringles. During the study she reported no gastrointestinal symptoms in the five day post-consumption periods. She did report a stomach ache on the morning of visit 3 but did participate in the study that day without any further problems.

Subject 450 is a 27 year old healthy male who only completed three of the four visits even after allowing him to have "make-up" visits because he did not keep his appointments. He initially called to report that he ate three ounces of Fat-Free Pringles chips on two consecutive days and experienced severe cramping, flatulence and indigestion and a discolored bowel movement within six hours of eating on the second day. He did not report any symptoms during the study after any of the three visits.

Subject 464 is a 78 year old healthy female who initially called to report experiencing bloating two hours after eating two ounces of Fat free Pringles on one day. The following day she ate four ounces of Fat free Pringles and had a soft bowel movement. A few days later she ate a few chips without affect. During the study she was compliant with consuming two ounces at each visit and reported no symptoms after any of the four visits.

Cohort 5

Subjects completing all four study visits

Nine subjects did not report gastrointestinal symptoms during the study.

Subject 502 is a 26 year old female taking Tagamet for heartburn and an "herbal allergy" medication who initially called to report that she experienced severe abdominal cramping and severe loose stool within 12 hours of eating "several" handfuls of BBQ WOW! Chips. She related that she has sharp abdominal cramping and diarrhea whenever she eats MSG. During the study she denied any symptoms after any of the four visits. It is of interest that she regularly consumed high fiber Slim Fast Shakes during her participation in the study.

Subject 506 is a 53 year old male with a history of gout taking colchicine and ibuprofen who initially called to report experiencing moderate diarrhea within 10 hours of eating three ounces of Fat free Pringles. During the study he denied any symptoms after any of the four visits.

Subject 507 is a 47 year old male who regularly takes Prozac who initially called to report experiencing an increase in soft bowel movements after eating two sample bags (one and a half ounces total) of WOW! Lay's and Doritos. During the study he denied any symptoms after any of the four visits.

Subject 508 is a 34 year old male who initially called to report experiencing severe abdominal cramping and heartburn within a few minutes of eating two ounces of WOW! Doritos. During the study he denied any symptoms after any of the four visits.

Subject 516 is a 50 year old male with a history of atrial fibrillation and heart disease taking Norvasc and aspirin who reports heartburn from eating spicy foods who initially called to report experiencing stomach cramping and loose stools within one hour of eating one ounce of WOW! Cool Ranch Doritos. Later that same evening he ate another ounce of WOW! Ruffles and had the same symptoms an hour later. He did not report any symptoms after any of the four visits.

Subject 519 is a 24 year old obese female with a history of Bipolar Affective Disorder taking Depakote who initially called to report experiencing severe cramping, diarrhea, and flatulence after eating six ounces of WOW! Lay's. The symptoms resolved within one day. She related that broccoli gives her similar gas symptoms. She described no symptoms after any of the four visits.

Subject 523 is a 52 year old female in good health who initially called to report that she experienced severe abdominal cramping six hours after eating six Fat free Pringles. She also reported a moderately swollen tongue after the following day. She described no symptoms after any of the four visits.

Six subjects reported symptoms after one eating occasion only.

Subject 500 is a 37 year old male with a history of low back problems who initially called to report experiencing moderate abdominal cramping within one and a half hours and loose stools within 12 hours of eating a total of 10 WOW! Ruffles. Symptoms resolved within two hours of when they occurred. During the study, he had symptoms after eating Ruffles WOW! at visit 3 when he complained of mild stomach cramping that started three hours after eating the chips and lasted two hours. He also complained of some abdominal cramping at visit 2 prior to eating the chips but had no complaints after eating the chips that day. He attributed the cramping that day to the heat.

Subject 509 is 41 year old female with a history of hypertension taking Maxide who is the managing editor for the Indianapolis Recorder. She wrote an article for the Indianapolis Recorder in May, 1997 and described that she had eaten about a half of a bag of WOW! chips and the next day developed a queasy feeling and a "feeling of being hung over". These symptoms continued for one week. Then she ate a few Ritz made with Olean and the queasiness continued. During the study, she reported symptoms on one occasion only. At visit 1, before eating Lays WOW! chips she stated that she was experiencing stomach rumbling which she attributed to having eaten Taco Bell foods that day. Nine hours later she described experiencing mild diarrhea.

Subject 513 is a 37 year old female on pain medication for a mending broken leg who first called to relate that she experienced severe diarrhea and cramping five hours after eating five ounces of WOW! Lay's chips. She took Imodium for her symptoms. She related that she has similar symptoms after eating spicy foods in general. During the study she had symptoms after eating Husman's full fat chips at visit 3 when she described moderate stomach cramps and sharp pains one hour after eating the chips.

Subject 514 is a 50 year old male in good health who initially called to report that he experienced severe cramping and mild loose stools after eating a sample (three quarters of an ounce) bag of WOW! Lay's. During the study he described symptoms only after eating Husman's full fat chips at visit 4 when he had mild stomach discomfort ninety minutes after eating the chips. He took two antacids and the symptoms resolved. He related that this made have been related to the other foods he ate that day which included chili.

Subject 515 is a 76 year old male with a history of hypertension on Zestril who first called to report that he experienced vomiting 30 minutes after eating two handfuls of WOW! Lay's. During the study he experienced symptoms only after visit 1 when he described "noise" from gas in his stomach 12 hours after eating Lays WOW! chips. The symptoms was rated as mild.

Subject 520 is a 62 year old female with a history of diabetes mellitus taking Humulin and Glucotrol who initially called to report experiencing severe gas after eating about seven ounces of WOW! Lay's. She took Tums for this symptom. She indicated that she has similar symptoms if she eats a large amount of beans. During the study she reported mild gas three hours after eating Lays WOW! chips at visit 2. Symptoms resolved within two hours.

Five subjects experienced gastrointestinal experiences two times during the study.

Subject 501 is a 29 year old male with a history of allergies and heartburn. The initial call to the company was made by his wife who reported that her husband had experienced diarrhea, nausea and stomach cramping within 15 hours of eating two ounces of Lay's WOW!. She related that his symptoms were severe. Interestingly, he related that he has had stomach cramps, loose stool and gas after eating large quantities of a variety of foods. During the study he described symptoms after two visits. After visit 2, when he ate Husman's full fat chips he described two incidences of loose stool 16 hours after eating the chips. He rated this event as mild. After visit 3, when he ate Ruffles full fat chips he described mild gas one hour after eating the chips.

Subject 510 is a 72 year old obese female with a history of hypertension, osteoporosis, and migraine headaches taking Lodine, Premarin and Synthroid who initially called to report experiencing severe bloating, severe diarrhea and greasy mouth-coat within five hours of eating one ounce of WOW! Lay's. She states that she is allergic to chocolate and regularly experiences heartburn when eating spicy foods. During the study she reported mild nausea three hours after eating Husman's full fat chips at visit 3 for which she took Mylanta. She also commented that she doesn't generally eat as many chips as we asked her to. After visit 4, she described moderate cramping and diarrhea that started within five hours of eating Lays WOW! chips. Symptoms resolved within a few hours without treatment.

Subject 517 is a 26 year old female with a history of headaches taking oral contraceptives who initially called to report that she experienced severe cramping, diarrhea and a headache a "couple" of hours after eating around three handfuls of WOW! Doritos. She went to the Emergency Department where they gave her Motrin. Symptoms lasted for three days. She stated that she had up to 15 bowel movements on a day. During the study she described moderate stomach cramping and mild diarrhea the day after eating Ruffles WOW! chips at visit 1. Symptoms lasted two hours. She also related that she had a headache that week but couldn't remember when. After visit 4 she described mild loose stools and mild cramping two days after eating Lays WOW! chips. Cramping resolved after 30 minutes when she had the bowel movement.

Subject 518 is an 11 year old female with a history of heartburn and headaches whose mother initially called to report that the child experienced severe cramping and diarrhea and moderate nausea after eating two handfuls of WOW! Doritos. She was treated with Gaviscon which is what she normally takes for heartburn. During the study she reported cramping for the first three weeks. After visit 1 she described moderate cramping 90 minutes after eating Husman's full fat chips. The symptoms lasted for two days. Prior to eating any product at visit 2 she described that she had had cramping that day. She did not have symptoms after eating the chips. The morning after visit 3, when she ate Lays WOW! chips, she woke up with cramping and remained in bed. Symptoms lasted for a day.

Subject 522 is a 56 year old female with a history of recent back surgery taking Advil for the pain who initially called to report experiencing diarrhea within 12 hours of eating a sample bag of WOW! Lay's (3/4 ounce). Symptoms were rated as severe and lasted for 17 hours. During the study she reported symptoms after two visits. Two hours after eating Husman's full fat chips at visit 1 she had mild lower abdominal cramping with an urge to defecate. She did not state that she had a BM. She also described that she had one bowel movement the following day that appeared darker in color than usual. During that week she took Darvocet for a headache. Two days after eating Lays WOW! chips at visit 2 she described that she had one episode of "soft bowels" which she attributed to eating chocolate candy which she does not normally eat.

<u>One subject experienced gastrointestinal symptoms three times during the study.</u>

Subject 511 is a 43 year old female with a history of esophageal reflux and seasonal allergies taking Claritin D who initially called to report experiencing severe abdominal pain within two hours of eating twenty WOW! Ruffles. Four hours after eating Ruffles full fat chips at visit 1 she described a mild "belly ache" that lasted for 30 minutes. She had several complaints after visit 2 when she described knee pain, mild pain in the lower abdomen that started two and a half hours after eating Lays WOW! chips, and mild stomach grumbling seven hours after eating the chips that lasted for 15 minutes. Three hours after eating Ruffles WOW! chips at visit 3 she described mild heartburn for which she took Zantac.

Cohort 6

Subjects completing all four study visits

<u>Five subjects did not report gastrointestinal symptoms during the study</u>

Subject 605 is a 65 year old female with a history of insulin-dependent diabetes mellitus and hypertension taking Humulin and Hydrochlorothiazide who initially called to report experiencing severe cramping and mild diarrhea within two hours of eating 20 Fat free Pringles. She reported no symptoms after any of the four consumption periods even though she stated that drinking any amount of milk will cause her to have gas.

Subject 606 is a 68 year old male with a history of congestive heart failure, atrial fibrillation and cardiomyopathy taking Coumadin, Lasix, Cordarone, Lanoxin, Vasotec and Synthroid who initially called to report experiencing a "gripey" stomach, diarrhea and urgency within three hours of eating one and a half ounces of WOW! Lay's Barbecue. He reported no symptoms after any of the four consumption periods.

Subject 611 is a 26 year old female in good health whose husband initially called to report that his wife experienced moderate bloating, diarrhea and "a tight stomach" which was rated as severe, within one hour of eating three samples of WOW! Lay's (3/4 ounce each, 2 ¼ ounces total). She reported no symptoms after any of the four consumption periods.

Subject 618 is a 52 year old male with a history of hypertension and hypercholesterolemia taking Inderal, Hydrodiuril, Mevacor, Cardura, and Lortab for pain secondary to foot surgery who initially called to report experiencing moderate cramping and loose stools within eight hours of eating WOW! Lay's daily for five consecutive days. On the first day he ate about two ounces and then for the next four days he ate a sample bag each day (3/4 ounce). During the study he had loose bowels only on the morning of visit 2 before eating the chips which he stated was due to his having eaten watermelon. He did not described symptoms after eating the chips at that visit.

Subject 621 is a 20 year old female in good health who initially called to report that she experienced moderate cramping, gas and loose stools within 12 hours of eating a sample bag (3/4 ounce) of WOW! Lay's. Of interest she related that eating red meat always gives her diarrhea. She did not report any symptoms within the five days of any consumption period. On the day of visit 4 she complained that she had mild stomach ache and cramping in the morning that had been more severe the day before. She did not report symptoms after eating the chips at visit 4.

Nine subjects reported gastrointestinal symptoms after one visit only.

Subject 600 is a 29 year old female who initially called to report experiencing severe gas, moderate diarrhea and mild abdominal cramping within one hour after eating 12 WOW! Doritos. During the study she described symptoms only after visit 1 when she had mild gas five hours after eating Ruffles WOW! chips. It is of interest that this subject reported that she has gas and indigestion after eating vegetables and dairy products.

Subject 602 is a 47 year old female with a history of depression and panic attacks taking Zoloft and Lorazepam who initially called to report experiencing moderate abdominal cramping within 3 hours of eating one and a half ounces of WOW! chips. During the study she was hospitalized six days after visit 1 (Ruffles full fat) after a three day illness with fever, shaking chills, headache, nausea, lower back pain and general malaise. She was discharged with a diagnosis of "walking pneumonia" and urinary tract infection. She continued in the study, completing all four visits with no further problems.

Subject 603 is a 28 year old male whose wife initially called to report that her husband experienced cramping and diarrhea within 12 hours of eating "several handfuls" of WOW! Lay's Barbecue chips. She volunteered that MSG also causes him to have these symptoms while pepperoni and Mexican food give him indigestion. During the study he reported symptoms only after visit 4 when he described two episodes of loose stools 12 hours after eating Ruffles full fat chips. This symptom was rated as mild.

Subject 608 is a 17 year old female with a history of depression taking Remeron who initially called to report experiencing cramping and diarrhea after eating three ounces of Fat free Pringles over two days. During the study she described symptoms of mild diarrhea and gas that occurred the day after she ate Husman's full fat chips at visit 2.

Subject 609 is a 29 year old female in good health taking oral contraceptives who initially called to report experiencing cramping, gas, loose stools, indigestion and abdominal pain, all rated as moderate, after she ate one handful each of two flavors of Fat free Pringles and WOW! Doritos. During the study she described symptoms only after visit 1 when she had mild loose stools one and a half hours after eating Ruffles full fat chips for which she took Pepto Bismol. The following day she stated she had mild gas.

Subject 610 is a 64 year old male in good health who initially called to report experiencing loose stools and urgency within two hours of eating three Fat free Pringles. During the study he described symptoms only after visit 4 when he stated that he had one loose bowel movement 24 hours after eating Lays WOW! chips.

Subject 615 is a 35 year old female taking oral contraceptives who initially called to report experiencing stomach cramping, urgency and loose stools within fifteen minutes of eating three quarters of an ounce of WOW! Ruffles. During the study she described symptoms only after visit 1 when she had mild cramping 15 minutes after eating Lays WOW! chips. The symptoms resolved in 15 minutes.

Subject 619 is an 11 year old male in good health whose mother initially called to report that her son experienced cramping, diarrhea, headache and nausea within ten hours of eating five ounces of WOW! Doritos. During the study he described that he "woke up not feeling well" one day during the week after eating Ruffles full fat chips at visit 1.

Subject 620 is a 23 year old male who reported experiencing severe abdominal pain, cramps and diarrhea after eating two ounces of Fat free Pringles. During the study he described one incident of mild diarrhea the day after he ate Ruffles full fat chips at visit 1.

<u>Five subjects reported gastrointestinal symptoms after two eating occasions.</u>

Subject 607 is a 35 year old male in good health whose friend initially called to report that he experienced cramping and diarrhea within six hours of eating one sample bag (3/4 ounce) of WOW! Lay's chips. During the study he described symptoms after two of the consumption periods. Two hours after eating Ruffles WOW! chips at visit 1 he described mild abdominal cramping that lasted for 30 minutes. Four hours after eating Husman's full fat chips at visit 3 he described moderate diarrhea and cramping.

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Subject 612 is a 42 year old obese female with a history with asthma, allergies and anxiety with stated intolerance to pineapple, oily foods, meat and dairy products who initially called to report experiencing cramps, loose stools and gas within three hours of eating 17 WOW! Ruffles. During the study she described symptoms after two of the consumption visits. Thirty minutes after eating Ruffles WOW! chips at visit 3 she described moderate gas that lasted for two hours. After visit 4, when she ate Husman's full fat chips, she described that she had a bowel movement that was not loose but it was unusual to have a bowel movement at that time of the day. In addition she experienced gas after eating the chips with the gas resolving when she had the bowel movement. Also during the study, she reported that she had an ear infection, swollen ankles, and shortness of breath. She was put on Augmentin and related that this gave her an upset stomach.

Subject 616 is a 56 year old female on hormone replacement therapy who initially called to report experiencing severe cramping and moderate diarrhea within one hour of eating four ounces of WOW! Lay's. During the study she described having mild gas two hours after eating Lays WOW! chips at visit 1 and mild cramping, diarrhea, and queasiness 12 hours after eating Ruffles WOW! chips at visit 4.

Subject 617 is a 53 year old male in good health whose wife initially called to report that her husband experienced diarrhea the day after eating three ounces of Fat free Pringles. During the study he reported mild diarrhea 11 hours after eating Ruffles full fat chips at visit 2, and moderate diarrhea 12 hours after eating Husman's full fat chips at visit 3.

Subject 624 is a 40 year old obese female with a history of depression for which she takes Zoloft and a "ruptured disc" for which she takes Darvocet who initially called to report experiencing severe cramping and diarrhea with moderate nausea within 20 minutes of eating three quarters of an ounce of WOW! Doritos. During the study she described symptoms after two visits. Eleven hours after eating Ruffles full fat chips at visit 1 she described mild stomach cramping with moderate diarrhea that lasted for two hours. Two hours after eating Ruffles WOW! chips at visit 3 she described moderate diarrhea.

<u>One subject reported gastrointestinal events after all four visits.</u>

Subject 622 is a 62 year old female with a history of a detached retina taking Timolol and atropine eye drops who initially called to report experiencing mild cramping and severe gas five hours after eating 12 WOW! chips. She reported some symptoms after each of the four consumption periods. She described three episodes of mild diarrhea 18 hours eating Ruffles WOW! chips at visit 1. She described mild gas two hours after eating Ruffles full fat chips at visit 2. Three hours after eating Husman's full fat chips at visit 3 she reported mild gas, stomach cramps, and one episode of loose stool. The day after visit 4, when she ate Lays WOW! chips, she described mild gas, diarrhea, and stomach cramps.

<u>Two subjects did not complete all four visits.</u>

Subject 601 is a 58 year old female with a history of hypertension, thyroid disease, and chronic obstructive pulmonary disease secondary to cigarette smoking and arthritis who initially called to

report experiencing severe diarrhea and abdominal pain within 12 hours of eating about one ounce of chips made with Olean. During the study she described no symptoms after visit 1 (Lay's WOW!) or visit 2 (Husman's) but within one hour of eating chips at visit 3 (Ruffles full fat) she developed diarrhea and experienced abdominal pain which lead to a hospitalization four days later (8/21/87). Her symptoms subsided and she was discharged on 8/23/97 with a diagnosis of enterocolitis of unknown etiology. She was readmitted to the hospital with the same symptoms on 9/5/97, laboratory screening was all within normal limits and it was noted that she did not have diarrhea in the hospital and she was discharged on 9/6/97 with a diagnosis of enterocolitis. Subsequent colonoscopy on 9/18/97 revealed diffuse diverticulosis with a narrowing at 60 cm. A brief summary of this subject's study participation was prepared by the study investigator, Dr. Winston Satterlee and is included in Appendix 2.

Subject 623 is a 26 year old female who had a cold when she entered the study. She initially called to report experiencing severe cramping within twenty hours of eating a three quarters of an of an ounce of WOW! Doritos. She completed only the first two visits and during that time was diagnosed with otitis media. She was withdrawn from the study because of failure to attend scheduled study visits.

Symptoms Reported Outside the 5 day Post-consumption Window and Non-Gastrointestinal Symptoms

All gastrointestinal symptoms reported for the five day window after each consumption were included in the analysis. There were only six reports of gastrointestinal symptoms outside the five day data window. In cohort 1, subject 200 stated her stomach felt a little queasy on the day of the second visit before she ate product. In cohort 4, Subject 444 reported a stomach ache on the morning of visit 3 but did participate in the study that day without any further problems. In Cohort 5, subject 500 reported stomach cramping the morning of visit 2 before eating any chips and went on to participate that day without any further problems; subject 518 reported experiencing cramping the morning of visit 2, participated in the study that day and had no further symptoms.

In cohort 6, Subject 618 reported loose bowel the morning of visit 2 which he associated with having eaten watermelon and subject 621 reported having a stomach ache and cramping the day before, and the morning of visit 4.

Non-gastrointestinal (Non-GI) symptoms were uncommon. No participants in cohort 1 reported non-GI symptoms. In cohort 2, Subject 120 described moderate headaches on several occasions after eating both full fat and chips made with olestra. Headaches were noted as a pre-existing condition prior to the study.

In cohort 3, subject 409 described being "shaky and dizzy" fifteen minutes after the third visit when she ate Lay's Max chips. It is of interest that she described similar symptoms in her initial report. Symptoms of this nature have not been associated with consumption of olestra in controlled clinical trials.

In cohort 4, Subject 421, a six year old boy, was reported by his mother to have a mild generalized rash that was first noted three days after visit 1. His mother called the boy's pediatrician and it was hypothesized that the rash was secondary to wearing a new sweat suit before it had been laundered. The rash resolved without treatment.

Subject 420 and 443 reported upper respiratory symptoms during the study. Subject 433 suffered traumatic injury to her mouth about one week after visit 2.

Concomitant Medications

Medications taken by participants prior to study initiation are listed in Exhibits 14a, 14b, 14c, 14d, 14e and 14 f for cohorts 1, 2, 3, 4, 5, and 6, respectively.

Medications taken for gastrointestinal symptoms: During the study, one participant, Subject 200 in cohort 1, took Imodium (loperamide) during the second treatment period on the day of dosing. Although she was not experiencing any alterations in bowel habits, she stated she took the Imodium as "she did not want to have diarrhea since she was having company that night".

Another participant, 121 in cohort 2, took Pepto-Bismol for diarrhea after the second visit and one participant, 407 in cohort 3 stated she took some Tums for stomach cramping after the second visit. In cohort 4, Subject 448 reported moderate diarrhea three to four hours after consuming Ruffles full fat chips at visit 3. She reported taking Pepto-Bismol.

In cohort 5, Subject 511 took Zantac for heartburn after the third visit when she ate Ruffles WOW! chips and subject 510 reported taking Mylanta for nausea after visit 3 when she ate Husman's full fat chips. In cohort 6, one participant, 609 took Pepto Bismol for loose stools after visit 1 when she ate Ruffles full fat chips and one participant, 616 reported taking Imodium for stomach cramps and diarrhea after visit 4 when she ate Ruffles WOW! chips.

Subject 601 was hospitalized for gastrointestinal complaints. A detailed description of her clinical course can be found in the Individual Consumer Experiences section of this report.

Medications taken for non-gastrointestinal symptoms: Subject 120 (cohort 2) took Aleve (Naprosyn) during the study for headaches which was a pre-existing condition as noted above. She had also been taking Paxil (paroxetine) which she stated was prescribed for headaches. Subject 420 reported upper respiratory symptoms for which he took Dimetapp and Tylenol. Subject 443 reported cold symptoms during the study and took Alka Seltzer Cold Formula. Subject 433 sustained a traumatic injury to her mouth a week after the second visit and was treated with a unspecified mouthwash and given a tetanus shot.

Subject 511 reported knee pain and took Tylenol. Subject 517 and 522 reported headache and took Excedrin and Darvocet, respectively. Subject 608 reported taking Zoloft for depression and Subject 612 reported taking Augmentin for an ear infection and Diamox for ankle swelling. Subject 623 reported cold symptoms and reported taking unspecified nose drops and an ear infection for which she was prescribed Zithromax.

Subject 602 was hospitalized for "walking pneumonia" and a urinary tract infection. A detailed description of her clinical course can be found in the Individual Consumer Experiences section of this report.

Discussion

Background

Olean is Procter & Gamble's brand of olestra, a non-absorbable, non-caloric fat substitute recently approved by the US FDA for use in the preparation of savory snack foods (e.g., potato chips, corn chips, extruded snacks and crackers). Olean is a mixture of octa-, hepta-, and hexa-fatty esters of sucrose with added vitamins produced utilizing processes common in the fats and oil industry.

Studies in animals and humans have demonstrated that olestra does not injure the gastrointestinal mucosa; does not result in malabsorption of carbohydrates, proteins, or fats; does not alter bile acid metabolism; does not result in significant changes in gastrointestinal transit; does not result in significant alterations in stool water or electrolyte content; is not metabolized by the colonic microflora; and does not cause a significant alteration in the colonic microflora.

Long-term feeding studies in dogs and pigs have demonstrated a dose-responsive increase in the frequency of pasty or loose stools without any increase in the frequency of watery stool even at daily exposures of olestra up to 8% of the diet by weight (10,11).

Studies in humans have demonstrated that after single eating occasions and typical snack eating simulations, there is little to no difference between the frequency of reporting of meaningful gastrointestinal symptoms or effects when consuming chips made with olestra or conventional fat. In a large, well-controlled study where 709 subjects consumed 34 grams/day of olestra for five consecutive days, there were no statistical differences in reporting rates of diarrhea, loose stools or abdominal cramping (12). In a recent double-blind, randomized study, 1136 participants, ranging in age from 13 to 88 years, ate as much as they wanted of a thirteen ounce bag of chips made with Olean or conventional fat. Gastrointestinal symptoms were monitored three to five days later. There was no difference in the incidence of reporting of gastrointestinal symptoms overall, or any individual gastrointestinal symptom (7).

In placebo-controlled studies where olestra was consumed in various foods at daily consumption levels of about 20 gram/day for sixteen weeks in 193 normal healthy subjects (2), and for four weeks in eighty persons with inflammatory bowel disease (5), there were no differences in reporting rates between the groups of any gastrointestinal symptoms including diarrhea or abdominal cramping, except for more reports of minor changes in stool frequency or stool character by subjects with inflammatory bowel disease when they ate foods made with olestra. Importantly, these changes were not characterized as diarrhea by these inflammatory bowel disease patients (5). In an extended-use, market simulation study where participants had chips available in the home for up to five months, there were no differences in rates of reports of diarrhea or abdominal cramping (13).

Two studies demonstrated an increase in the reported incidence of gastrointestinal symptoms. They were the eight-week chronic dosing studies, where subjects were required to consume foods made with olestra at each meal for 56 consecutive days (168 consecutive meals) at daily

doses of 8, 20 and 32 g/d (3,4). In these studies there were increases in abdominal cramping and diarrhea/loose stools reported by some individuals consuming 20 and 32 grams/day. Symptom onset, when it was noted, was generally observed after several days of olestra consumption. Symptoms were usually not constant, but would come and go, with the exception of a few individuals who reported mild to moderate symptoms during most of the study. All persons describing chronic symptoms were evaluated by the physician at the study site and found to have normal physical examinations and normal laboratory findings (i.e., no evidence of dehydration or electrolyte disturbance). It is noteworthy that no one elected to drop from these studies because of loose stools, diarrhea, abdominal pain or cramping. Although these symptoms were increased in the 8 week studies at the 20 and 32 gram/day consumption level, it is worth noting that in a 14-day study conducted concurrently at a different site but at the same doses of olestra fed at every meal, there was no dose-related increase in abdominal cramping or diarrhea (6).

Key Findings From This Study

The Rechallenge Study enrolled individuals who had called the manufacturers' 800-line to report symptoms that they associated with consuming Olean chips. Of the ninety-eight consumers who participated in this study to date, 88 (90%) had initially called to report that they had experienced diarrhea, and/or loose stool, and/or abdominal cramping. This is representative of the total pool of callers, 86% of whom reported these symptoms. When these individuals were formally tested in this Rechallenge Study, there were no differences in the number of reports of symptoms after individuals consumed Olean chips compared to when they consumed full fat chips. Thus, the response of these individuals to repeated exposures of chips made with Olean and conventional fat in a masked fashion, does not support an association of any clinically meaningful symptoms with Olean snack consumption under free-living conditions even in a self-selected population.

The following discussion examines individual symptoms reported during the study and compares these symptoms to those that occurred pre-study, which were spontaneously reported to the manufacturers.

Diarrhea and/or loose stool: There were no differences in the number or severity of reports of diarrhea or loose stools when subjects ate Olean chips compared to when they ate full fat chips. Fifty-nine of the participants in the study had initially called to report diarrhea; 23 (23%) reports were stated to be "severe", while 15 were moderate. During participation in this study, 24 subjects reported diarrhea (10* after eating chips made with Olean and fifteen* after eating full fat chips), and 23 subjects reported having loose stool (10 after eating chips made with Olean and 13 after eating full fat chips). There were two reports of severe diarrhea and those were by participants after eating full fat chips. There were equal numbers of reports of moderate diarrhea and/or loose stools after subjects ate full fat or Olean chips. These results refute that Olean chip consumption at a single eating occasion will cause an increase in rates of diarrhea, even in a self-selected population who had previously reported this symptom.

* One subject (624) reported diarrhea after full fat and Olean chip consumptions.

Abdominal cramping: There were no differences when subjects were eating Olean chips compared to when they ate full fat chips. Fifty-nine of the participants in the study had initially reported cramping when they called the manufacturer; with 27 reports (28%) rated as severe and eighteen as moderate. However, during the study there were no differences in the overall frequency of reports of cramping. Although severe symptoms were rarely reported in this study, there were numerically more severe or moderate cramping reports when participants had eaten full fat chips compared to when they had eaten Olean chips.

While it is reassuring that there was no increase in the frequency or severity of gastrointestinal symptoms when subjects consumed Olean chips compared to when they consumed full fat chips, it is important to understand whether there were other differences in the characteristics of symptoms when they did occur. For example, are there meaningful differences in characteristics such as time to symptom onset? This examination is particularly relevant for reports of abdominal cramping as reports of severe or unusual cramping that occur shortly after ingestion of olestra were not anticipated from the pre-approval clinical data set but have been reported in calls to the 800-lines. If there was a subset of the population in whom Olean chips would cause unusual cramping, then rechallenging these individuals would be expected to provoke symptoms of cramping as initially reported. The following discussion examines in detail reports of cramping from consumers in their initial call to the manufacturer and when they participated in the Rechallenge Study.

The available information does not provide evidence that Olean chip consumption provokes abdominal cramping when subjects ate Olean chips compared to when they ate full fat chips. This is demonstrated by examining the onset and severity for reports of abdominal cramping during the study and comparing those results to the experiences initially reported by the consumers when they called the 800-lines. Forty-nine (50%) of the participants in this study had initially called to report that they had "acute" abdominal cramping with 21 rating their symptoms as "severe". (For the purposes of this discussion, "acute" is defined as within 12 hours of when they ate the Olean chips). Only 19 of these 49 subjects went on to report cramping at any time during the Rechallenge Study. Fifteen people reported mild cramping, 11 after eating Olean chips and five after eating full fat chips, while four reported moderate cramping, two after eating full fat and two after Olean chips. It is worth noting that only six of the 21 subjects who initially called to report "severe" cramping, that they attributed to eating Olean chips, went on to report any cramping during their participation in the study.

The lack of any meaningful differences in the characteristics of cramping, with regard to incidence, severity, and even time of onset does not support that eating Olean chips at a single eating occasion will cause an increase in the rate of abdominal cramping; nor does it support that Olean chip consumption has a unique capacity to cause unusual cramping symptoms in a subgroup of individuals. Rather, the fact that 15 out of the 21 consumers in the study who had initially called to report experiencing "severe" cramping did not report any cramping after eating two ounces of Olean chips on two separate occasions speaks against such an association. There was one report of mild cramping after one eating occasion of Olean chips by a consumer who initially reported severe cramping. In a study of this size and design this finding may very well be a chance event.

The Phenomenon of False Attribution of Common Symptoms to the Diet

In the present study, we are addressing whether persons who have spontaneously reported gastrointestinal symptoms they attributed to eating Olean-containing snacks, including symptoms of diarrhea and cramping, would have these symptoms if they ate a two ounce serving of Olean-containing chips again in a masked fashion. A randomized, double-blinded placebo-controlled design was employed to address this question, as there is considerable difficulty in identifying constituents of the diet that cause digestive symptoms. This fact was recently well demonstrated by Suarez et al. (14), when they conducted a randomized, double-blind, cross-over trial of milk in people who self-reported having severe lactose intolerance. In their study, 30 people were enrolled who reported having severe lactose intolerance with symptoms of abdominal pain, bloating, flatulence and/or diarrhea consistently resulting after ingesting even small amounts of milk. The investigators gave the study participants 2% milk or 2% lactose-hydrolyzed milk plus an artificial sweetener (Equal) to correct for the change in taste (the strength of masking treatment differences was verified prior to the study). The investigators reported that even though studies without placebo controls in similar populations had reported up to 60% of subjects having symptoms after drinking eight ounces of milk, they found that gastrointestinal symptoms reported by subjects in the controlled environment were minimal with no significant difference in any symptoms between the two periods when they drank eight ounces of milk. The investigators suggested that a subset of subjects with an underlying tendency towards symptoms may be misattributing their abdominal symptoms to lactose intolerance. They were particularly impressed by the apparent minor nature of symptoms reported by this group that had claimed they had severe intolerance.

Another example of confusion about diet-induced symptoms followed the widespread use of aspartame in beverages in the 1980s which provoked a number of consumer complaints, 517 of which were investigated by the Centers for Disease Control (CDC). Over two-thirds of these reports involved the neurologic system, especially headaches; while most of the remainder of the reports (24%) were common gastrointestinal complaints of abdominal pain, nausea, diarrhea and vomiting (15, 16). Experimental studies in rodents suggested that at high doses of aspartame, the phenylalanine metabolite of the artificial sweetener could alter brain concentrations of neurotransmitter amines which might explain the neurologic effects described by consumers. During this time there had been considerable negative press about the safety and the neurologic effects of aspartame consumption which may have provoked the level of reporting (16). Schiffman et al. (17) conducted a well-controlled, double-blind study in forty of the consumers who had reported repeated headaches following the ingestion of products containing aspartame. They found that the incidence of headache after short-term challenge was equivalent to that after placebo. The CDC concluded that the symptoms being reported were generally mild in nature and were symptoms which occur commonly in the general population (16).

The study by Suarez highlights the false attribution of a variety of abdominal symptoms to lactose intolerance. It also suggests that people may tend to exaggerate their symptoms in an anecdotal setting but be more likely to report their experiences accurately during a controlled study. The study by Schiffman demonstrates the potential for false attribution of headaches and common gastrointestinal complaints to a controversial food additive. With commonly occurring subjective symptoms like headaches and gastrointestinal complaints, there may be a tendency to

attribute symptoms to consumption of foods others have found or stated to be problematic. The fact is that lactose intolerance is fairly common in adults particularly when very large amounts are ingested. What is rarely appreciated is that even lactose "intolerant" persons can tolerate an eight ounce serving of milk; however, most people are not aware of this; they only know that drinking milk can make some people have symptoms.

Because olestra is a non-absorbed fat, it is reasonable to expect that it could, if consumed in sufficient quantity over a sufficient period of time, produce a laxative-like effect in some individuals. Dose-associated gastrointestinal symptoms have been demonstrated with olestra consumption in some but not all of the clinical studies where subjects were required to consume olestra with every meal for weeks at a time. There are, however, no data to support that consumers will experience an increased incidence of gastrointestinal symptoms when they eat olestra snacks under typical snacking conditions. Unfortunately, the current label does not provide this perspective, and this confusion may account for the high level of reporting of diarrhea and cramping even at consumption levels as low as a few chips and after single eating occasions.

Whether the Olean-consumers who called to report symptoms actually experienced more severe symptoms that prompted their initial call to the manufacturer compared to the symptoms they reported during the study, or whether there is simply a decreased likelihood of symptoms' being categorized as severe in a controlled testing situation, as was seen in the study by Suarez (14), cannot be ascertained from this study; but these dilemmas are of continuing import to food manufacturers and regulatory authorities. For diarrhea, loose stools, and abdominal cramping, symptom frequency and severity reported by the ninety-eight subjects was similar between the two treatments supporting that there was false attribution of symptoms in the initial reporting.

Perspective Relative to the Passive Post-Marketing Surveillance Database

The goal of this study was to rechallenge a representative sample of individuals, who called with gastrointestinal complaints, employing testing circumstances designed to simulate the average consumer chip-eating occasion that prompted consumers to call. The following discussion outlines why participants in this study are representative of the overall population of consumers who called the 800-lines.

During the period covered by this study, the manufacturers (P&G and Frito-Lay) had received reports of gastrointestinal symptoms from 1,134 consumers, 1,100 of whom had called to report experiencing gastrointestinal symptoms as a result of consuming snacks made with olestra. Consequently, the 98 subjects included in rechallenge to date comprise nearly 9% of the total pool of consumers eligible to participate. This compares favorably to the published aspartame rechallenge study where forty persons participated out of a pool of just over 500 consumers who had reported experiencing aspartame-induced symptoms (15, 16, 17).

The single eating occasion setting was an appropriate test setting as greater than 75% of the calls to the snack manufacturers during the period covered by this study, and in fact for the first year of market availability, were from consumers who called to report that they experienced symptoms after a single eating occasion. This compared favorably to the group of study participants; 77% reported eating the Olean chips on a single occasion.

The participants in this study to date are quite comparable to the overall pool of consumers who have called with respect to type and severity of symptoms. Over 85% of the calls received have claimed that consumption of the product resulted in diarrhea, loose stool, or abdominal cramping. Forty-three percent of the callers self-rated their symptoms as "severe" relative to other symptoms they had experienced in the past. This compares favorably to the study participants, of whom 90% had initial complaints of diarrhea, loose stool, and/or cramping with 40% of these symptoms being rated as severe.

The participants in the Rechallenge Study were also typical based upon the quantity of chips they consumed that prompted their initial call. Relative to the amount of Olean consumed that prompted the consumer's initial call to the manufacturers, 63 of the consumers in this study reported having eaten less than 16.4 grams of Olean (equivalent to two ounces of Olean potato chips), seven reported eating 16.8 to 20 grams of Olean, and 25 ate more than this amount with a range of 25 to 61 grams, and one subject reported eating 153 grams of Olean over two days. For the remaining two participants, their initial consumption is unknown. The amount of chips provided at each visit in this study was two ounces (16.8 grams of olestra). Consequently, nearly three quarters of this self-selected group of participants were rechallenged with a comparable or greater amount of Olean, without evidence that Olean snacks were any more likely to be associated with these types of complaints than when consumers are eating full fat chips as a part of their diet. In fact, for 40% of the participants, the two-ounce consumption was twice as much or more than what they had originally stated caused their gastrointestinal symptoms.

Gastrointestinal symptoms are very common in the general population. The findings of Drossman have been substantiated by a Computer Aided Telephone cross-sectional population survey "U.S. National Survey of Digestive Complaints" conducted by Innovative Medical Research, between August 11 and October 6, 1997*. Among 2,510 adults interviewed, 1,017 (40.5%) reported one or more digestive symptoms within the month prior to the survey. Abdominal pain was reported by 21.8%, bloating by 15.9%, and loose stools by 26.9%. More than 70% rated their symptoms as moderate or severe in intensity and more than 20% had greater than 25% limitation in daily activities. Among those with symptoms, more than 20% reported they experienced these symptoms in the previous twenty-four hours, 9-19% went to see a physician and nearly 50% took medications. These data are consistent with the published work

* An abstract of this study has been prepared by IMR and Dr. Robert Sandler for submission to the Annual Meetings of the American Gastroenterological Association (AGA), May 16-22, 1998. The data in this paragraph was taken from the abstract. Innovative Medical Research is planning to file their full report to the Office of Scientific Support, FDA, in January, 1997.

of Drossman et al. (19), which demonstrated that over half of the people surveyed had some gastrointestinal symptoms within a three month period. The high rates of background gastrointestinal complaints in the population puts in perspective how false attribution may occur, especially in an environment of controversy when a product's safety is being questioned. It is certainly worth noting that 70% of the participants in this study reported some gastrointestinal symptoms at some time during the four weeks of the study and 58% of all reports were claimed to have occurred within the 24 hours following the consumption periods.

The recently completed Acute Consumption Study (a.k.a. The Theater Test) also demonstrates that gastrointestinal symptoms are quite common in routine circumstances and those that occurred after eating Olean chips may be erroneously thought to be "caused" by eating Olean. Considering that there were no differences in reported gastrointestinal symptoms in this Rechallenge Study when comparing reports after eating Olean chips to reports after eating full fat chips, there is no support for a causal association between eating Olean chips and symptoms. Rather this finding suggests that consumers who called the manufacturers may have misattributed their background symptoms to the fact that they had recently eaten chips made with Olean.

The importance of the Rechallenge Study is that it further explores whether there are individuals in the population at large who are, for whatever reason, particularly intolerant to consuming Olean. It is possible that such individuals may not have been evident from the controlled, large-base clinical testing but could only be identified in the post-marketing environment with significantly larger numbers of people exposed. The participants in the Rechallenge Study are self-selected individuals who had called to relate symptoms which they attributed to having eaten snacks made with Olean. They are a reasonably representative sample of the total pool of consumers who called during the first nine months of the test markets. If there were a subgroup in the general population who could be categorized as "sensitive" to consuming olestra, recruitment of study participants from the total pool of consumers calling the 800-lines should result in higher levels of symptom reporting among then when they blindly consumed olestra compared to subjects in the olestra clinical studies who are not pre-selected based upon their assessment of olestra tolerance. The group of 98 who participated in the Rechallenge Study did in fact frequently report gastrointestinal symptoms during the study, but at no greater incidence nor of greater severity when they were eating Olean chips than when they were eating full fat chips. This result suggests that these individuals themselves, and as a representative group of the total pool of callers, could not reasonably be categorized as "sensitive" to Olean.

Conclusions

Although all 98 of these participants had initially reported symptoms that they attributed to eating chips made with Olean, the numbers of people reporting symptoms after eating either Olean chips or full fat chips were comparable. While 48% of these participants (compared to 44% of the total pool of consumers who called) described severe symptoms that prompted their initial call to the manufacturer when asked to rate their symptoms against other experiences they had in the past, no participants experienced severe symptoms upon rechallenge with Olean chips when asked to rate their symptoms as mild, moderate, or severe, according to the impact the symptoms had on their usual daily activities.

In this self-selected population, there were no differences between the number of reports of abdominal cramping, diarrhea, and/or loose stool after eating Olean chips compared to after eating full fat chips. These results suggest that false attribution of commonly occurring gastrointestinal symptoms is not uncommon. Comparison with other published studies where individuals with common symptoms are rechallenged, demonstrates that this phenomena is not unique to Olean snacks. There is no evidence from this study that there is a subgroup of "sensitive" individuals in the population who would experience clinically meaningful symptoms following consumption of Olean snack in a typical snacking setting.

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Signatures

Investigator	Date
Nora L. Zmuda	1/29/98
Project Physician	Date
Thomas A Fillo	1/29/98
Project Statistician	Date

Signatures

Winston Satterlee, MD	1-28-98
Investigator	Date
Project Physician	Date
Project Statistician	Date

EXHIBITS

Exhibit 1

Cohorts 1 through 6

Treatment Assignments for each Cohort

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
100	1	F2	O1	F1	O2
101	1	O2	F1	O1	F2
102	1	O1	O2	F2	F1
200	1	F2	O1	F1	O2
201	1	O2	F1	O1	F2
202	1	O1	O2	F2	F1
203	1	F1	F2	O2	O1
204	1	F1	F2	O2	O1
300	1	F2	F1	O1	O2
301	1	O2	F1	O1	F2
302	1	F1	F2	O2	O1
120	2	F1	O1	O2	F2
121	2	F2	O2	O1	F1
220	2	F1	O1	O2	F2
221	2	F2	O2	O1	F1
320	2	O2	F1	F2	O1
321	2	F2	O2	O1	F1
400	3	F2	F1	O1	O2
401	3	F1	O2	F2	O1
402	3	O1	F2	O2	F1
403	3	O2	O1	F1	F2
404	3	O2	O1	F1	F2
405	3	F2	F1	O1	O2
406	3	F1	O2	F2	O1
407	3	O1	F2	O2	F1
408	3	O2	O1	F1	F2
409	3	O1	F2	O2	F1

Exhibit 1 - (cont'd)

Cohorts 1 through 6

Treatment Assignments for each Cohort

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
420	4	F2	O2	O1	F1
421	4	O2	O1	F1	F2
423	4	F1	F2	O2	O1
424	4	O1	F1	F2	O2
425	4	F1	F2	O2	O1
426	4	O2	O1	F1	F2
427	4	F2	O2	O1	F1
428	4	F1	F2	O2	O1
429	4	O2	O1	F1	F2
430	4	F2	O2	O1	F1
431	4	O1	F1	F2	O2
432	4	F1	F2	O2	O1
433	4	O1	F1	F2	O2
434	4	F2	O2	O1	F1
435	4	O2	O1	F1	F2
436	4	O2	O1	F1	F2
437	4	F2	O2	O1	F1
438	4	O1	F1	F2	O2
440	4	F2	O2	O1	F1
441	4	F1	F2	O2	O1
442	4	O1	F1	F2	O2
443	4	O2	O1	F1	F2
444	4	O2	O1	F1	F2
445	4	O1	F1	F2	O2
446	4	F1	F2	O2	O1
447	4	F2	O2	O1	F1
448	4	O1	F1	F2	O2
449	4	F1	F2	O2	O1
450	4	O2	O1	F1	F2
464	4	F1	F2	O2	O1

Exhibit 1 - (cont'd)

Cohorts 1 through 6

Treatment Assignments for each Cohort

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
500	5	F2	O2	O1	F1
501	5	O2	F1	F2	O1
502	5	O1	F2	F1	O2
506	5	F2	O2	O1	F1
507	5	F1	O1	O2	F2
508	5	F1	O1	O2	F2
509	5	O2	F1	F2	O1
510	5	O1	F2	F1	O2
511	5	F2	O2	O1	F1
513	5	O1	F2	F1	O2
514	5	F2	O2	O1	F1
515	5	O2	F1	F2	O1
516	5	O2	F1	F2	O1
517	5	O1	F2	F1	O2
518	5	F1	O1	O2	F2
519	5	F2	O2	O1	F1
520	5	F2	O2	O1	F1
522	5	F1	O2	F2	O1
523	5	F1	O1	O2	F2
600	6	O1	F2	F1	O2
601	6	O2	F1	F2	O1
602	6	F2	O2	O1	F1
603	6	F1	O1	O2	F2
605	6	O2	F1	F2	O1
606	6	F1	O1	O2	F2
607	6	O1	F2	F1	O2
608	6	O2	F1	F2	O1
609	6	F2	O2	O1	F1
610	6	O1	F2	F1	O2
611	6	F1	O1	O2	F2
612	6	F2	O2	O1	F1
615	6	O2	O2	F2	F1
616	6	O2	F1	F2	O1
617	6	O1	F2	F1	O2
618	6	F1	O1	O2	F2

Exhibit 1 - (cont'd)

Cohorts 1 through 6

Treatment Assignments for each Cohort

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
619	6	F2	O2	O1	F1
620	6	F2	O2	O1	F1
621	6	O2	F1	F2	O1
622	6	O1	F2	F1	O2
623	6	F1	O1	O2	F2
624	6	F2	O2	O1	F1

Exhibit 2

Cohorts 1 through 6
Subject Age

Age	Subjects	
	Participating n (%)	Total Population n (%)
Less than 10	1 (1%)	117 (10%)
10-19	6 (6%)	90 (9%)
20-49	58 (59%)	588 (52%)
50-79	33 (34%)	256 (23%)
> 79	0 (0%)	7 (1%)
Unknown	0 (0%)	76 (7%)
Total	98	1,134*

* The total population of consumers who called the 800-lines. This number includes those people who were not eligible to participate because they did not meet protocol inclusion criteria.

Exhibit 3

Cohorts 1 through 6
Subject Sex

Sex	Subjects	
	Participating	Total Population
	n (%)	n (%)
Male	31 (32%)	413 (36%)
Female	67 (68%)	721 (64%)
Total	98	1,134*

* The total population of consumers who called the 800-lines. This number includes those people who were not eligible to participate because they did not meet protocol inclusion criteria

Exhibit 4a

Cohort 1
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
100/GAL	Stools loose Cramp abdomen[2]	3.2
101/BEB	Cramp abdomen[3] Diarrhea	5.6
102/RSS	Cramp abdomen[2]	40.5
200/JRC	Cramp abdomen[2] Diarrhea	7.4
201/MLB	Diarrhea Stomach queasy	8.1 over 3 days
202/CAM	Eructation Upset stomach Flatulence Aftertaste	20.0
203/TJS	Cramp abdomen[3] Diarrhea BM Urgency	9.6
204/SSM	Diarrhea	45.6 38.0 7.6

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4a - (cont'd)

Cohort 1
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
300/JCB	Diarrhea	14.8
		7.4
		7.4
	Abdominal Pain	
301/MEA	Stools loose	29.6
	Flatulence	
	Bloating	
302/CGR	Diarrhea	7.5

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4b

Cohort 2
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
120/VML	Diarrhea Cramp abdomen	3.8
121/SAT	Cramp abdomen[2]	16.2
220/RES	Cramp abdomen Diarrhea	16.2
221/JMV	Flatulence[2] Stools loose[2] Burning rectum[3]	42.0 over 7 days
320/VAG	Flatulence[1] Pain upper abdomen[1]	6.1
321/VAM	Nausea	3.0

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4c

Cohort 3
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
400/AJT	Stools loose[1]	50.7
	Discolor stool[1]	12.6
	Oily stool[1]	25.5
	Oil in toilet[1]	12.6
401/PJM	Cramp abdomen[2]	3.4
	Diarrhea[2]	
	BM Urgency	
402/WDO	Stools loose[2]	3.5
	Flatulence	1.5
	Discolor stool	1.0
	Headache	1.0
403/MAW	Diarrhea	10.0
	Cramp abdomen	
	Headache	
	Nausea	
	Bloating	

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4c - (cont'd)

Cohort 3
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
404/TWB	Cramp abdomen[3]	18.0
	Diarrhea[3]	5.0
		2.5
		2.5
		8.0
405/CSM	Cramp abdomen[1]	50.4
	Diarrhea[3]	42.0
		8.4
406/MMS	Cramp abdomen[2]	9.0
	Diarrhea[2]	6.0
	Stools Loose	3.0
407/AST	Cramp abdomen[2]	4.0
408/MSN	Diarrhea[2]	7.5
409/JLK	Dizziness	UNK
	Shakiness	
	Tunnel vision	

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4d

Cohort 4
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
420/RES	Cramp abdomen[3] Diarrhea[3] BM Urgency[3]	6.0
421/CMP	Diarrhea[3]	UNK
423/EXD	Cramp abdomen[1] Diarrhea[1]	6.0
424/JAL	Cramp abdomen[1] Gas in stomach[1] Bloating[1] Aftertaste[1]	12.0 6.0 6.0
425/WHE	Aftertaste Diarrhea[1]	12.6
426/MBG	Upset stomach[3] Diarrhea[2] Stomach ache	51.0 25.5 25.5
427/NBW	Stools loose[1]	153 over 2 days

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4d - (cont'd)

Cohort 4
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
428/MBS	Cramp abdomen[3]	50.4
429/JKC	Diarrhea[1] Cramp abdomen[2]	33.6
430/LAV	Diarrhea[3]	8.4
431/JPB	Diarrhea[2]	25.5
432/DLJ	Cramp abdomen[3] Diarrhea[3]	25.2
433/RAK	Pain lower abdomen[3] Bloody diarrhea	5.0
434/BJS	Diarrhea[2] Cramp abdomen[2] Upset stomach[2]	16.8
435/ALM	Cramp abdomen[1]	2.5
436/CKO	Stools loose[2] Headache	10.5 1.0 6.0 3.5
437/JMB	Diarrhea[3]	16.8

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4d - (cont'd)

Cohort 4
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
438/TLL	Diarrhea[1]	9.5
	Pain stomach[2]	7.5
	Nausea[3]	1.0
		1.0
440/JER	Diarrhea[3]	26.7
		1.5
		25.2
441/MLR	Cramp abdomen[3]	12.6
	Flatulence[3]	
	Diarrhea[2]	
442/CAH	Diarrhea[3]	25.5
443/BLJ	Cramp abdomen[3]	12.5
444/AMF	Diarrhea[2]	5.0
	Vomiting[3]	
445/MSJ	Diarrhea[2]	4.0
	Cramp abdomen[2]	
	Flatulence[3]	
	Bloating[3]	

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4d - (cont'd)

Cohort 4
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
446/MMS	Cramp abdomen[1]	5.0
447/RAC	Diarrhea[3]	3.0
	Flatulence[3]	
	Cramp abdomen[3]	
448/RMK	Cramp abdomen[3]	33.6
	Diarrhea[3]	
449/RLO	Diarrhea[3]	5.0
	Cramp abdomen[2]	
450/MJT	Diarrhea[3]	51.0
	Flatulence	25.5
	Cramp abdomen[3]	25.5
	Indigestion	
	Discolor stool	
464/LRM	Bloating	50.4
	Diarrhea	4.0
		33.6
		16.8

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4e

Cohort 5
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
500/DES	Cramp abdomen[2] Stools loose[2]	3.0
501/TSD	Cramp abdomen[3] Nausea[2] Diarrhea[3]	16.2
502/ALF	Diarrhea[3] Stools loose[3]	10.5
506/DLD	Diarrhea[2]	50.4
507/PDM	Stool soft[1]	12.2
508/ERR	Cramp abdomen[3], Burning in abdomen[3]	10.0
509/CGH	Queasy[2] Hangover effect[2]	60.8
510/RSC	Bloating[3] Diarrhea[3]	8.1
511/SRG	Abdominal pain[3]	6.0
513/PAM	Cramp abdomen[3] Diarrhea[3]	42.3

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4e – (cont'd)

Cohort 5
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
514/JWL	Stools loose[1] Cramp abdomen[3]	10.8
515/RHR	Vomiting[3]	7.4
516/JDH	Cramp Abdomen[1] Diarrhea[1]	8.1
517/CLM	Cramp abdomen[3] Diarrhea[3]	10.2
518/RRM	Cramp abdomen[3]	6.4
519/JEM	Cramp abdomen[3] Diarrhea[3] Flatulence[3]	48.6
520/PLM	Flatulence[3]	61.0
522/YHM	Diarrhea[3]	6.1
523/CSM	Cramp abdomen[3] Tongue edema[2]	3.0

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4f

Cohort 6
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
600/NSP	Flatulence[3] Diarrhea[2] Cramp abdomen[1]	6.0
601/SSS	Cramp abdomen[3] Diarrhea[3]	7.3
602/JMW	Cramp abdomen[2]	unknown
603/TRF	Cramp abdomen[3] Diarrhea[3]	10.5
605/BJT	Cramp abdomen[3] Diarrhea[1]	10.0
606/JWS	Abdominal pain[1] Diarrhea[1]	11.4
607/RKH	Cramp abdomen (unknown) Diarrhea (unknown)	6.1
608/JNT	Cramp abdomen (unknown) Diarrhea (unknown)	25.2

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4f - (cont'd)

Cohort 6
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
609/CML	Flatulence[2] Stools loose[2] Pain stomach[2] Cramp abdomen[2] Indigestion[2]	5.3
610/TJS	Stools loose[1]	1.5
611/MID	Pain stomach[3] Bloating[2] Diarrhea[2]	18.2
612/PRJ	Flatulence[2] Cramp abdomen[2] Loose stool[2]	5.1
615/EMW	Cramp abdomen[1] Stools loose[1] BM urgency (unknown)	6.1
616/E-B	Cramp abdomen[3] Diarrhea[2]	32.4
617/WAM	Diarrhea (unknown)	25.2
618/JJB	Cramp abdomen[2] Stools loose[2]	39.1

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 4f - (cont'd)

Cohort 6
Listing of All Subject Symptoms From Original Reports

Subject ID and Initials	Original Report: Symptom(s)	Original Report: Dose* (grams of olestra)
619/JJB	Diarrhea[2] Cramp abdomen[2] Nausea[1] Headache[1]	28.0
620/CRH	Cramp abdomen[3] Diarrhea[2] Abdomen pain[3]	16.8
621/TCB	Cramp abdomen[2] Flatulence[2] Diarrhea[1]	6.1
622/SJS	Cramp abdomen[1] Flatulence[3]	3.6
623/JAH	Cramp abdomen[3]	4.2
624/CLK	Diarrhea[3] Cramp abdomen[3] Nausea[2]	4.2

[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported
*Most reports involved consumption on only one day. If consumption occurred over more than one day, the total consumption is listed first with the individual daily consumption listed beneath.

Exhibit 5

Occurrence of GI Symptoms by Visit

ANY GI Symptom

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
100	1	F2	O1	F1	O2
101	1	O2	F1	O1	F2
102	1	O1	O2	F2	F1
200	1	F2	O1	F1	O2
201	1	O2	F1	O1	F2
202	1	O1	O2	F2	F1
203	1	F1	F2	O2	O1
204	1	F1	F2	O2	O1
300	1	F2	F1	O1	O2
301	1	O2	F1	O1	F2
302	1	F1	F2	O2	O1
120	2	F1	O1	O2	F2
121	2	F2	O2	O1	F1
220	2	F1	O1	O2	F2
221	2	F2	O2	O1	F1
320	2	O2	F1	F2	O1
321	2	F2	O2	O1	F1
400	3	F2	F1	O1	O2
401	3	F1	O2	F2	O1
402	3	O1	F2	O2	F1
403#	3	O2			
404	3	O2	O1	F1	F2
405	3	F2	F1	O1	O2
406	3	F1	O2	F2	O1
407	3	O1	F2	O2	F1
408	3	O2	O1	F1	F2
409	3	O1	F2	O2	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 5- (cont'd)

Occurrence of GI Symptoms by Visit

ANY GI Symptom

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
420	4	F2	O2	O1	F1
421	4	O2	O1	F1	F2
423	4	F1	F2	O2	O1
424	4	O1	F1	F2	O2
425	4	F1	F2	O2	O1
426	4	O2	O1	F1	F2
427	4	F2	O2	O1	F1
428	4	F1	F2	O2	O1
429	4	O2	O1	F1	F2
430	4	F2	O2	O1	F1
431	4	O1	F1	F2	O2
432#	4	F1			
433#	4	O1	F1		
434	4	F2	O2	O1	F1
435	4	O2	O1	F1	F2
436	4	O2	O1	F1	F2
437	4	F2	O2	O1	F1
438	4	O1	F1	F2	O2
440	4	F2	O2	O1	F1
441	4	F1	F2	O2	O1
442	4	O1	F1	F2	O2
443	4	O2	O1	F1	F2
444	4	O2	O1	F1	F2
445	4	O1	F1	F2	O2
446	4	F1	F2	O2	O1
447	4	F2	O2	O1	F1
448	4	O1	F1	F2	O2
449	4	F1	F2	O2	O1
450#	4	O2	O1	F1	
464	4	F1	F2	O2	O1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 5- (cont'd)

Occurrence of GI Symptoms by Visit

ANY GI Symptom					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
500	5	F2	O2	O1	F1
501	5	O2	F1	F2	O1
502	5	O1	F2	F1	O2
506	5	F2	O2	O1	F1
507	5	F1	O1	O2	F2
508	5	F1	O1	O2	F2
509	5	O2	F1	F2	O1
510	5	O1	F2	F1	O2
511	5	F2	O2	O1	F1
513	5	O1	F2	F1	O2
514	5	F2	O2	O1	F1
515	5	O2	F1	F2	O1
516	5	O2	F1	F2	O1
517	5	O1	F2	F1	O2
518	5	F1	O1	O2	F2
519	5	F2	O2	O1	F1
520	5	F2	O2	O1	F1
522	5	F1	O2	F2	O1
523	5	F1	O1	O2	F2
600	6	O1	F2	F1	O2
601#	6	O2	F1	F2	
602	6	F2	O2	O1	F1
603	6	F1	O1	O2	F2
605	6	O2	F1	F2	O1
606	6	F1	O1	O2	F2
607	6	O1	F2	F1	O2
608	6	O2	F1	F2	O1
609	6	F2	O2	O1	F1
610	6	O1	F2	F1	O2
611	6	F1	O1	O2	F2
612	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 5- (cont'd)

Occurrence of GI Symptoms by Visit

ANY GI Symptom					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
615	6	O2	O2	F2	F1
616	6	O2	F1	F2	O1
617	6	O1	F2	F1	O2
618	6	F1	O1	O2	F2
619	6	F2	O2	O1	F1
620	6	F2	O2	O1	F1
621	6	O2	F1	F2	O1
622	6	O1	F2	F1	O2
623#	6	F1	O1		
624	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 6

Occurrence of GI Symptoms by Visit

ABDOMINAL CRAMPING

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
100	1	F2	O1	F1	O2
101	1	O2	F1	O1	F2
102	1	O1	O2	F2	F1
200	1	F2	O1	F1	O2
201	1	O2	F1	O1	F2
202	1	O1	O2	F2	F1
203	1	F1	F2	O2	O1
204	1	F1	F2	O2	O1
300	1	F2	F1	O1	O2
301	1	O2	F1	O1	F2
302	1	F1	F2	O2	O1
120	2	F1	O1	O2	F2
121	2	F2	O2	O1	F1
220	2	F1	O1	O2	F2
221	2	F2	O2	O1	F1
320	2	O2	F1	F2	O1
321	2	F2	O2	O1	F1
400	3	F2	F1	O1	O2
401	3	F1	O2	F2	O1
402	3	O1	F2	O2	F1
403#	3	O2			
404	3	O2	O1	F1	F2
405	3	F2	F1	O1	O2
406	3	F1	O2	F2	O1
407	3	O1	F2	O2	F1
408	3	O2	O1	F1	F2
409	3	O1	F2	O2	F1

F = Full fat , O = Olean

F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max

Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits

Shading denotes Occurrence of GI symptom

Exhibit 6 - (cont'd)

Occurrence of GI Symptoms by Visit

ABDOMINAL CRAMPING

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
420	4	F2	O2	O1	F1
421	4	O2	O1	F1	F2
423	4	F1	F2	O2	O1
424	4	O1	F1	F2	O2
425	4	F1	F2	O2	O1
426	4	O2	O1	F1	F2
427	4	F2	O2	O1	F1
428	4	F1	F2	O2	O1
429	4	O2	O1	F1	F2
430	4	F2	O2	O1	F1
431	4	O1	F1	F2	O2
432#	4	F1			
433#	4	O1	F1		
434	4	F2	O2	O1	F1
435	4	O2	O1	F1	F2
436	4	O2	O1	F1	F2
437	4	F2	O2	O1	F1
438	4	O1	F1	F2	O2
440	4	F2	O2	O1	F1
441	4	F1	F2	O2	O1
442	4	O1	F1	F2	O2
443	4	O2	O1	F1	F2
444	4	O2	O1	F1	F2
445	4	O1	F1	F2	O2
446	4	F1	F2	O2	O1
447	4	F2	O2	O1	F1
448	4	O1	F1	F2	O2
449	4	F1	F2	O2	O1
450#	4	O2	O1	F1	
464	4	F1	F2	O2	O1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 6 - (cont'd)

Occurrence of GI Symptoms by Visit

ABDOMINAL CRAMPING

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
500	5	F2	O2	O1	F1
501	5	O2	F1	F2	O1
502	5	O1	F2	F1	O2
506	5	F2	O2	O1	F1
507	5	F1	O1	O2	F2
508	5	F1	O1	O2	F2
509	5	O2	F1	F2	O1
510	5	O1	F2	F1	O2
511	5	F2	O2	O1	F1
513	5	O1	F2	F1	O2
514	5	F2	O2	O1	F1
515	5	O2	F1	F2	O1
516	5	O2	F1	F2	O1
517	5	O1	F2	F1	O2
518	5	F1	O1	O2	F2
519	5	F2	O2	O1	F1
520	5	F2	O2	O1	F1
522	5	F1	O2	F2	O1
523	5	F1	O1	O2	F2
600	6	O1	F2	F1	O2
601#	6	O2	F1	F2	
602	6	F2	O2	O1	F1
603	6	F1	O1	O2	F2
605	6	O2	F1	F2	O1
606	6	F1	O1	O2	F2
607	6	O1	F2	F1	O2
608	6	O2	F1	F2	O1
609	6	F2	O2	O1	F1
610	6	O1	F2	F1	O2
611	6	F1	O1	O2	F2
612	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 6 - (cont'd)

Occurrence of GI Symptoms by Visit

ABDOMINAL CRAMPING

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
615	6	O2	O2	F2	F1
616	6	O2	F1	F2	O1
617	6	O1	F2	F1	O2
618	6	F1	O1	O2	F2
619	6	F2	O2	O1	F1
620	6	F2	O2	O1	F1
621	6	O2	F1	F2	O1
622	6	O1	F2	F1	O2
623#	6	F1	O1		
624	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 7

Occurrence of GI Symptoms by Visit

DIARRHEA

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
100	1	F2	O1	F1	O2
101	1	O2	F1	O1	F2
102	1	O1	O2	F2	F1
200	1	F2	O1	F1	O2
201	1	O2	F1	O1	F2
202	1	O1	O2	F2	F1
203	1	F1	F2	O2	O1
204	1	F1	F2	O2	O1
300	1	F2	F1	O1	O2
301	1	O2	F1	O1	F2
302	1	F1	F2	O2	O1
120	2	F1	O1	O2	F2
121	2	F2	O2	O1	F1
220	2	F1	O1	O2	F2
221	2	F2	O2	O1	F1
320	2	O2	F1	F2	O1
321	2	F2	O2	O1	F1
400	3	F2	F1	O1	O2
401	3	F1	O2	F2	O1
402	3	O1	F2	O2	F1
403#	3	O2			
404	3	O2	O1	F1	F2
405	3	F2	F1	O1	O2
406	3	F1	O2	F2	O1
407	3	O1	F2	O2	F1
408	3	O2	O1	F1	F2
409	3	O1	F2	O2	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 7 - (cont'd)

Occurrence of GI Symptoms by Visit

DIARRHEA					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
420	4	F2	O2	O1	F1
421	4	O2	O1	F1	F2
423	4	F1	F2	O2	O1
424	4	O1	F1	F2	O2
425	4	F1	F2	O2	O1
426	4	O2	O1	F1	F2
427	4	F2	O2	O1	F1
428	4	F1	F2	O2	O1
429	4	O2	O1	F1	F2
430	4	F2	O2	O1	F1
431	4	O1	F1	F2	O2
432#	4	F1			
433#	4	O1	F1		
434	4	F2	O2	O1	F1
435	4	O2	O1	F1	F2
436	4	O2	O1	F1	F2
437	4	F2	O2	O1	F1
438	4	O1	F1	F2	O2
440	4	F2	O2	O1	F1
441	4	F1	F2	O2	O1
442	4	O1	F1	F2	O2
443	4	O2	O1	F1	F2
444	4	O2	O1	F1	F2
445	4	O1	F1	F2	O2
446	4	F1	F2	O2	O1
447	4	F2	O2	O1	F1
448	4	O1	F1	F2	O2
449	4	F1	F2	O2	O1
450#	4	O2	O1	F1	
464	4	F1	F2	O2	O1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 7 - (cont'd)

Occurrence of GI Symptoms by Visit

DIARRHEA

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
500	5	F2	O2	O1	F1
501	5	O2	F1	F2	O1
502	5	O1	F2	F1	O2
506	5	F2	O2	O1	F1
507	5	F1	O1	O2	F2
508	5	F1	O1	O2	F2
509	5	O2	F1	F2	O1
510	5	O1	F2	F1	O2
511	5	F2	O2	O1	F1
513	5	O1	F2	F1	O2
514	5	F2	O2	O1	F1
515	5	O2	F1	F2	O1
516	5	O2	F1	F2	O1
517	5	O1	F2	F1	O2
518	5	F1	O1	O2	F2
519	5	F2	O2	O1	F1
520	5	F2	O2	O1	F1
522	5	F1	O2	F2	O1
523	5	F1	O1	O2	F2
600	6	O1	F2	F1	O2
601#	6	O2	F1	F2	
602	6	F2	O2	O1	F1
603	6	F1	O1	O2	F2
605	6	O2	F1	F2	O1
606	6	F1	O1	O2	F2
607	6	O1	F2	F1	O2
608	6	O2	E1	F2	O1
609	6	F2	O2	O1	F1
610	6	O1	F2	F1	O2
611	6	F1	O1	O2	F2
612	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 7 - (cont'd)

Occurrence of GI Symptoms by Visit

DIARRHEA					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
615	6	O2	O2	F2	F1
616	6	O2	F1	F2	O1
617	6	O1	F2	F1	O2
618	6	F1	O1	O2	F2
619	6	F2	O2	O1	F1
620	6	F2	O2	O1	F1
621	6	O2	F1	F2	O1
622	6	O1	F2	F1	O2
623#	6	F1	O1		
624	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 8

Occurrence of GI Symptoms by Visit

LOOSE STOOLS

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
100	1	F2	O1	F1	O2
101	1	O2	F1	O1	F2
102	1	O1	O2	F2	F1
200	1	F2	O1	F1	O2
201	1	O2	F1	O1	F2
202	1	O1	O2	F2	F1
203	1	F1	F2	O2	O1
204	1	F1	F2	O2	O1
300	1	F2	F1	O1	O2
301	1	O2	F1	O1	F2
302	1	F1	F2	O2	O1
120	2	F1	O1	O2	F2
121	2	F2	O2	O1	F1
220	2	F1	O1	O2	F2
221	2	F2	O2	O1	F1
320	2	O2	F1	F2	O1
321	2	F2	O2	O1	F1
400	3	F2	F1	O1	O2
401	3	F1	O2	F2	O1
402	3	O1	F2	O2	F1
403#	3	O2			
404	3	O2	O1	F1	F2
405	3	F2	F1	O1	O2
406	3	F1	O2	F2	O1
407	3	O1	F2	O2	F1
408	3	O2	O1	F1	F2
409	3	O1	F2	O2	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 8 - (cont'd)

Occurrence of GI Symptoms by Visit

LOOSE STOOLS

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
420	4	F2	O2	O1	F1
421	4	O2	O1	F1	F2
423	4	F1	F2	O2	O1
424	4	O1	F1	F2	O2
425	4	F1	F2	O2	O1
426	4	O2	O1	F1	F2
427	4	F2	O2	O1	F1
428	4	F1	F2	O2	O1
429	4	O2	O1	F1	F2
430	4	F2	O2	O1	F1
431	4	O1	F1	F2	O2
432#	4	F1			
433#	4	O1	F1		
434	4	F2	O2	O1	F1
435	4	O2	O1	F1	F2
436	4	O2	O1	F1	F2
437	4	F2	O2	O1	F1
438	4	O1	F1	F2	O2
440	4	F2	O2	O1	F1
441	4	F1	F2	O2	O1
442	4	O1	F1	F2	O2
443	4	O2	O1	F1	F2
444	4	O2	O1	F1	F2
445	4	O1	F1	F2	O2
446	4	F1	F2	O2	O1
447	4	F2	O2	O1	F1
448	4	O1	F1	F2	O2
449	4	F1	F2	O2	O1
450#	4	O2	O1	F1	
464	4	F1	F2	O2	O1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 8 - (cont'd)

Occurrence of GI Symptoms by Visit

LOOSE STOOLS

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
500	5	F2	O2	O1	F1
501	5	O2	F1	F2	O1
502	5	O1	F2	F1	O2
506	5	F2	O2	O1	F1
507	5	F1	O1	O2	F2
508	5	F1	O1	O2	F2
509	5	O2	F1	F2	O1
510	5	O1	F2	F1	O2
511	5	F2	O2	O1	F1
513	5	O1	F2	F1	O2
514	5	F2	O2	O1	F1
515	5	O2	F1	F2	O1
516	5	O2	F1	F2	O1
517	5	O1	F2	F1	O2
518	5	F1	O1	O2	F2
519	5	F2	O2	O1	F1
520	5	F2	O2	O1	F1
522	5	F1	O2	F2	O1
523	5	F1	O1	O2	F2
600	6	O1	F2	F1	O2
601#	6	O2	F1	F2	
602	6	F2	O2	O1	F1
603	6	F1	O1	O2	F2
605	6	O2	F1	F2	O1
606	6	F1	O1	O2	F2
607	6	O1	F2	F1	O2
608	6	O2	F1	F2	O1
609	6	F2	O2	O1	F1
610	6	O1	F2	F1	O2
611	6	F1	O1	O2	F2
612	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 8 - (cont'd)

Occurrence of GI Symptoms by Visit

LOOSE STOOLS

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
615	6	O2	O2	F2	F1
616	6	O2	F1	F2	O1
617	6	O1	F2	F1	O2
618	6	F1	O1	O2	F2
619	6	F2	O2	O1	F1
620	6	F2	O2	O1	F1
621	6	O2	F1	F2	O1
622	6	O1	F2	F1	O2
623#	6	F1	O1		
624	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 9

Occurrence of GI Symptoms by Visit

DIARRHEA or LOOSE STOOLS

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
100	1	F2	O1	F1	O2
101	1	O2	F1	O1	F2
102	1	O1	O2	F2	F1
200	1	F2	O1	F1	O2
201	1	O2	F1	O1	F2
202	1	O1	O2	F2	F1
203	1	F1	F2	O2	O1
204	1	F1	F2	O2	O1
300	1	F2	F1	O1	O2
301	1	O2	F1	O1	F2
302	1	F1	F2	O2	O1
120	2	F1	O1	O2	F2
121	2	F2	O2	O1	F1
220	2	F1	O1	O2	F2
221	2	F2	O2	O1	F1
320	2	O2	F1	F2	O1
321	2	F2	O2	O1	F1
400	3	F2	F1	O1	O2
401	3	F1	O2	F2	O1
402	3	O1	F2	O2	F1
403#	3	O2			
404	3	O2	O1	F1	F2
405	3	F2	F1	O1	O2
406	3	F1	O2	F2	O1
407	3	O1	F2	O2	F1
408	3	O2	O1	F1	F2
409	3	O1	F2	O2	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 9 - (cont'd)

Occurrence of GI Symptoms by Visit

DIARRHEA or LOOSE STOOLS

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
420	4	F2	O2	O1	F1
421	4	O2	O1	F1	F2
423	4	F1	F2	O2	O1
424	4	O1	F1	F2	O2
425	4	F1	F2	O2	O1
426	4	O2	O1	F1	F2
427	4	F2	O2	O1	F1
428	4	F1	F2	O2	O1
429	4	O2	O1	F1	F2
430	4	F2	O2	O1	F1
431	4	O1	F1	F2	O2
432#	4	F1			
433#	4	O1	F1		
434	4	F2	O2	O1	F1
435	4	O2	O1	F1	F2
436	4	O2	O1	F1	F2
437	4	F2	O2	O1	F1
438	4	O1	F1	F2	O2
440	4	F2	O2	O1	F1
441	4	F1	F2	O2	O1
442	4	O1	F1	F2	O2
443	4	O2	O1	F1	F2
444	4	O2	O1	F1	F2
445	4	O1	F1	F2	O2
446	4	F1	F2	O2	O1
447	4	F2	O2	O1	F1
448	4	O1	F1	F2	O2
449	4	F1	F2	O2	O1
450#	4	O2	O1	F1	
464	4	F1	F2	O2	O1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 9 - (cont'd)

Occurrence of GI Symptoms by Visit

DIARRHEA or LOOSE STOOLS

Subject	Cohort	Visit 1	Visit 2	Visit 3	Visit 4
500	5	F2	O2	O1	F1
501	5	O2	F1	F2	O1
502	5	O1	F2	F1	O2
506	5	F2	O2	O1	F1
507	5	F1	O1	O2	F2
508	5	F1	O1	O2	F2
509	5	O2	F1	F2	O1
510	5	O1	F2	F1	O2
511	5	F2	O2	O1	F1
513	5	O1	F2	F1	O2
514	5	F2	O2	O1	F1
515	5	O2	F1	F2	O1
516	5	O2	F1	F2	O1
517	5	O1	F2	F1	O2
518	5	F1	O1	O2	F2
519	5	F2	O2	O1	F1
520	5	F2	O2	O1	F1
522	5	F1	O2	F2	O1
523	5	F1	O1	O2	F2
600	6	O1	F2	F1	O2
601#	6	O2	F1	F2	
602	6	F2	O2	O1	F1
603	6	F1	O1	O2	F2
605	6	O2	F1	F2	O1
606	6	F1	O1	O2	F2
607	6	O1	F2	F1	O2
608	6	O2	F1	F2	O1
609	6	F2	O2	O1	F1
610	6	O1	F2	F1	O2
611	6	F1	O1	O2	F2
612	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 9 - (cont'd)

Occurrence of GI Symptoms by Visit

DIARRHEA or LOOSE STOOLS					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
615	6	O2	O2	F2	F1
616	6	O2	F1	F2	O1
617	6	O1	F2	F1	O2
618	6	F1	O1	O2	F2
619	6	F2	O2	O1	F1
620	6	F2	O2	O1	F1
621	6	O2	F1	F2	O1
622	6	O1	F2	F1	O2
623#	6	F1	O1		
624	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 10

Occurrence of GI Symptoms by Visit

GAS (Eructation, Flatulence, Bloating)					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
100	1	F2	O1	F1	O2
101	1	O2	F1	O1	F2
102	1	O1	O2	F2	F1
200	1	F2	O1	F1	O2
201	1	O2	F1	O1	F2
202	1	O1	O2	F2	F1
203	1	F1	F2	O2	O1
204	1	F1	F2	O2	O1
300	1	F2	F1	O1	O2
301	1	O2	F1	O1	F2
302	1	F1	F2	O2	O1
120	2	F1	O1	O2	F2
121	2	F2	O2	O1	F1
220	2	F1	O1	O2	F2
221	2	F2	O2	O1	F1
320	2	O2	F1	F2	O1
321	2	F2	O2	O1	F1
400	3	F2	F1	O1	O2
401	3	F1	O2	F2	O1
402	3	O1	F2	O2	F1
403#	3	O2			
404	3	O2	O1	F1	F2
405	3	F2	F1	O1	O2
406	3	F1	O2	F2	O1
407	3	O1	F2	O2	F1
408	3	O2	O1	F1	F2
409	3	O1	F2	O2	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 10 - (cont'd)

Occurrence of GI Symptoms by Visit

GAS (Eructation, Flatulence, Bloating)					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
420	4	F2	O2	O1	F1
421	4	O2	O1	F1	F2
423	4	F1	F2	O2	O1
424	4	O1	F1	F2	O2
425	4	F1	F2	O2	O1
426	4	O2	O1	F1	F2
427	4	F2	O2	O1	F1
428	4	F1	F2	O2	O1
429	4	O2	O1	F1	F2
430	4	F2	O2	O1	F1
431	4	O1	F1	F2	O2
432#	4	F1			
433#	4	O1	F1		
434	4	F2	O2	O1	F1
435	4	O2	O1	F1	F2
436	4	O2	O1	F1	F2
437	4	F2	O2	O1	F1
438	4	O1	F1	F2	O2
440	4	F2	O2	O1	F1
441	4	F1	F2	O2	O1
442	4	O1	F1	F2	O2
443	4	O2	O1	F1	F2
444	4	O2	O1	F1	F2
445	4	O1	F1	F2	O2
446	4	F1	F2	O2	O1
447	4	F2	O2	O1	F1
448	4	O1	F1	F2	O2
449	4	F1	F2	O2	O1
450#	4	O2	O1	F1	
464	4	F1	F2	O2	O1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 10 - (cont'd)

Occurrence of GI Symptoms by Visit

GAS (Eructation, Flatulence, Bloating)					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
500	5	F2	O2	O1	F1
501	5	O2	F1	F2	O1
502	5	O1	F2	F1	O2
506	5	F2	O2	O1	F1
507	5	F1	O1	O2	F2
508	5	F1	O1	O2	F2
509	5	O2	F1	F2	O1
510	5	O1	F2	F1	O2
511	5	F2	O2	O1	F1
513	5	O1	F2	F1	O2
514	5	F2	O2	O1	F1
515	5	O2	F1	F2	O1
516	5	O2	F1	F2	O1
517	5	O1	F2	F1	O2
518	5	F1	O1	O2	F2
519	5	F2	O2	O1	F1
520	5	F2	O2	O1	F1
522	5	F1	O2	F2	O1
523	5	F1	O1	O2	F2
600	6	O1	F2	F1	O2
601#	6	O2	F1	F2	
602	6	F2	O2	O1	F1
603	6	F1	O1	O2	F2
605	6	O2	F1	F2	O1
606	6	F1	O1	O2	F2
607	6	O1	F2	F1	O2
608	6	O2	F1	F2	O1
609	6	F2	O2	O1	F1
610	6	O1	F2	F1	O2

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Exhibit 10 - (cont'd)

Occurrence of GI Symptoms by Visit

GAS (Eructation, Flatulence, Bloating)					
Subject	**Cohort**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
611	6	F1	O1	O2	F2
612	6	F2	O2	O1	F1
615	6	O2	O2	F2	F1
616	6	O2	F1	F2	O1
617	6	O1	F2	F1	O2
618	6	F1	O1	O2	F2
619	6	F2	O2	O1	F1
620	6	F2	O2	O1	F1
621	6	O2	F1	F2	O1
622	6	O1	F2	F1	O2
623#	6	F1	O1		
624	6	F2	O2	O1	F1

F = Full fat , O = Olean
F1 = Husman's, F2 = Ruffles, O1 = Ruffles Max, O2 = Lay's Max
# Subjects 403, 432, 433, 450, 601 and 623 did not complete all of their scheduled visits
Shading denotes Occurrence of GI symptom

Occurrence of Gastrointestinal Symptoms After Consumption of Olean and Triglyceride

[n = 98 subjects]

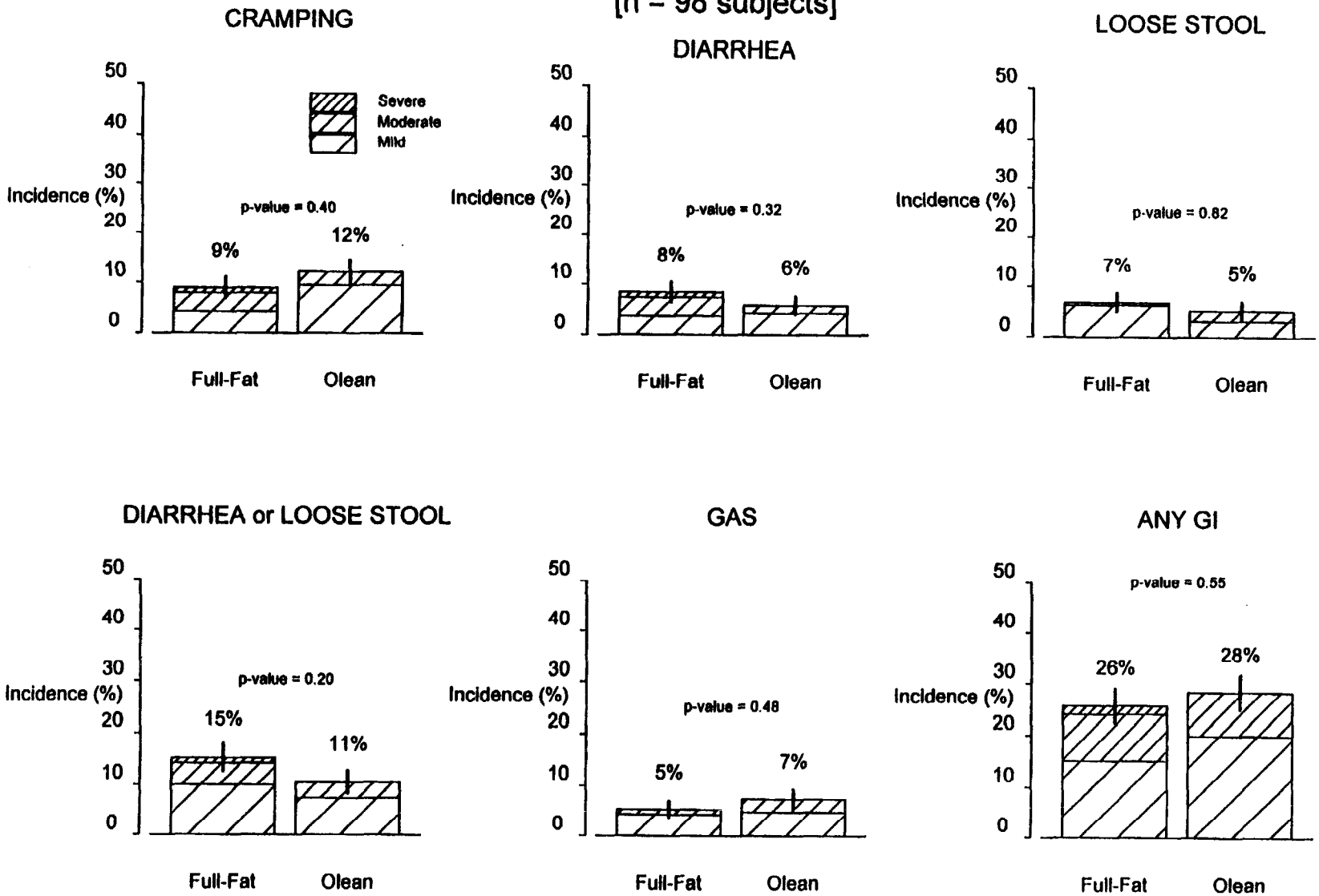

Exhibit 11

Exhibit 12a

Cohort 1
Listing of All Subject Symptoms From Day-3 Phone Interview

Subject ID and Initials	Day-3 Phone Interview Report Symptom(s) O1	Symptom(s) O2	Symptom(s) F1	Symptom(s) F2
100/GAL	Upset stomach[1]			
101/BEB			Cramp abdomen[2]	Cramp abdomen[2] Diarrhea[2]
102/RSS				
200/JRC	Flatulence[2]	Cramp abdomen[2] Nausea[2]		
201/MLB	Flatulence[1] Cramp abdomen[1]	Pain gas[1] Cramp abdomen[1] BM Urgency[1]		
202/CAM	Eructation[1]			
203/TJS				
204/SSM			Cramp abdomen[1] Stools loose[1]	
300/JCB		Bloating[2] Gas[2] Diarrhea[2] Loose Stools[2]		

F = Full fat , O = Olean
F1 = Husman , F2 = Ruffles , O1 = Ruffles Max, O2 = Lay's Max
[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported

Exhibit 12b

Cohort 2
Listing of All Subject Symptoms From Day-3 Phone Interview

Subject ID and Initials	Day-3 Phone Interview Report: Symptom(s) O1	Symptom(s) O2	Symptom(s) F1	Symptom(s) F2
120/VML			Stomach cramp[2] Diarrhea[2]	
121/SAT		Stomach cramp[1] Diarrhea[1]		
220/RES				
221/JMV				Cramping[2]
320/VAG			Diarrhea[1]	
321/VAM				

F = Full fat , O = Olean
F1 = Husman , F2 = Ruffles , O1 = Ruffles Max, O2 = Lay's Max
[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported

Exhibit 12c

Cohort 3
Listing of All Subject Symptoms From Day-3 Phone Interview

Subject ID and Initials	Day-3 Phone Interview Report Symptom(s) O1	Symptom(s) O2	Symptom(s) F1	Symptom(s) F2
400/AJT	Cramp abdomen[2]		Stools loose[1]	
401/PJM		Cramp abdomen[1] BM urgency[1]		
402/WDO	Stool freq. Increase[2]	Stool freq. Increase[2] Stools loose[2]		
403/MAW	*Not completed*		*Not completed*	*Not completed*
404/TWB				
405/CSM			Cramp abdomen[1] Diarrhea[1]	
406/MMS	Cramp abdomen[1]		Stools soft[1]	Stools loose[2]
407/AST			Cramp abdomen[1]	Cramp abdomen[1]
408/MSN	Flatulence[1]			Flatulence[2]
409/JLK		Cramp abdomen[1] Dizziness[2] Shakiness[1]		

F = Full fat , O = Olean
F1 = Husman , F2 = Ruffles , O1 = Ruffles Max, O2 = Lay's Max
[1]Severity reported as mild
[2]Severity reported as moderate
[2]Severity reported as severe
No superscript if severity not reported

Exhibit 12d

Cohort 4
Listing of All Subject Symptoms From Day-3 Phone Interview

Subject ID and Initials	Day-3 Phone Interview Report Symptom(s) O1	Symptom(s) O2	Symptom(s) F1	Symptom(s) F2
420/RES		Upset stomach[1]		
421/CMP			Flatulence[1] Stools loose[1]	
423/EXD				
424/JAL	Gas in stomach[1] Bloating[1]			
425/WHE				
426/MBG			Stomach ache[1]	
427/NBW				
428/MBS	Nausea[1]		Stools loose[1] Nausea[2]	
429/JKC		BM urgency[1] Stools loose[1]		
430/LAV	Stools loose[1]	Abdominal pain[1] Stools loose[1]		Inc. in BM Freq.[1] Stools loose[1]
431/JPB	Flatulence[2] Stools loose[2]	Flatulence[1]		Flatulence[1]
432/DJL	*Not completed*	*Not completed*	BM urgency[1] Stools loose[1] Borborygmus[1]	*Not completed*
433/RAK		*Not completed*	Diarrhea[1] Cramp abdomen[3]	*Not completed*
434/BJS	Stools loose[1]		Cramp abdomen[1] Diarrhea[2]	Stools loose[1]

F = Full fat , O = Olean
F1 = Husman , F2 = Ruffles , O1 = Ruffles Max, O2 = Lay's Max
[1]Severity reported as mild
[2]Severity reported as moderate
[2]Severity reported as severe
No superscript if severity not reported

Exhibit 12e

Cohort 5
Listing of All Subject Symptoms From Day-3 Phone Interview

Subject ID and Initials	Day-3 Phone Interview Report Symptom(s) O1	Symptom(s) O2	Symptom(s) F1	Symptom(s) F2
500/DES	cramp abdomen[1]			
501/TSD			stools loose[1]	flatulence[1]
502/ALF				
506/DLD				
507/PDM				
508/ERR				
509/CGH		diarrhea[1] queasy[2]		
510/RSC		cramp abdomen[2] diarrhea[2]	nausea[1]	
511/SRG	heartburn[1]	stomach ached[1] borborygmus[1]		abdominal pain[1]
513/PAM			cramp abdomen[2] upset stomach[1] pain stomach[2]	
514/JWL			dyspepsia[1]	
515/RHR		borborygmus[1]		
516/JDH				
517/CLM	cramp abdomen[2] diarrhea[1]	stools loose [1] cramp abdomen[1]		
518/RRM		cramp abdomen[2]	cramp abdomen[1]	
519/JEM				
520/PLM		flatulence[1]		
522/YHM		stool soft[1]	cramp abdomen[1] discoloration stool[1]	
523/CSM				

F = Full fat , O = Olean
F1 = Husman , F2 = Ruffles , O1 = Ruffles Max, O2 = Lay's Max
[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported

Exhibit 12f

Cohort 6
Listing of All Subject Symptoms From Day-3 Phone Interview

Subject ID and Initials	Day-3 Phone Interview Report Symptom(s) O1	Symptom(s) O2	Symptom(s) F1	Symptom(s) F2
600/NSP	flaulence[1]			
601/SSS				cramp abdomen[3] diarrhea[3]
602/JMW				nausea[2]
603/TRF				stools loose[1]
605/BJT				
606/JWS				
607/RKH	cramp abdomen[1]		diarrhea[2] cramp abdomen[2]	
608/JNT			diarrhea[1] flatulence[1]	
609/CML				flatulence[1] stools loose[1]
610/TJS		stools loose[1]		
611/MID				
612/PRJ	flatulene[2]	distress gastro[2] nausea[2]	flatulence[2] stool frequency increse[2]	
615/EMW		cramp abdomen[1]		
616/E-B	cramp abdomen[1] diarrhea[1] queasy[1]	flaulence[1]		
617/WAM			diarrhea[2]	diarrhea[1]
618/KEC				

F = Full fat , O = Olean
F1 = Husman , F2 = Ruffles , O1 = Ruffles Max, O2 = Lay's Max
[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported

Exhibit 12f (cont'd)

Cohort 6
Listing of All Subject Symptoms From Day-3 Phone Interview

Subject ID and Initials	Day-3 Phone Interview Report Symptom(s) O1	Symptom(s) O2	Symptom(s) F1	Symptom(s) F2
619/JJB				
620/CRH				diarrhea[1]
621/TCB				
622/SJS	diarrhea[1]	flatulence[1] diarrhea[1] cramp abdomen[1]	flatulence[1] cramp abdomen[1] stools loose[1]	
623/LAH				
624/CLK	diarrhea[2]			cramp abdomen[1] diarrhea[2]

F = Full fat , O = Olean
F1 = Husman , F2 = Ruffles , O1 = Ruffles Max, O2 = Lay's Max
[1]Severity reported as mild
[2]Severity reported as moderate
[3]Severity reported as severe
No superscript if severity not reported

Exhibit 13

Listing of Subject Numbers and Alert Case Numbers

Cohort 1		Cohort 2		Cohort 3	
Subject Number	ALERT Case No.	Subject Number	ALERT Case No.	Subject Number	ALERT Case No.
100	1300103	120	1300095	400	1300219
101	1300026	121	1300139	401	1300252
102	1300067	220	1300007	402	1300225
200	1300079	221	1300108	403	1300233
201	1300059	320	1300164	404	1300287
202	1300069	321	1300047	405	1300277
203	1300010			406	1300254
204	1300065			407	1300245
300	1300017			408	1300207
301	1300054			409	1300197
302	1300014				

Exhibit 13 - (cont'd)

Listing of Subject Numbers and Alert Case Numbers

Cohort 4		Cohort 5		Cohort 6	
Subject Number	ALERT Case No.	Subject Number	ALERT Case No.	Subject Number	ALERT Case No.
420	1300512	500	1300946	600	1300701
421	1300480	502	1300948	601	1301151
423	1300426	506	1331040	602	1300596
424	1300425	507	1300666	603	1300949
425	1300561	508	1300600	605	1301006
426	1300379	509	1301168	606	1300604
427	1300545	510	1300763	607	1300643
428	1300392	511	1300678	608	1301039
429	1300477	513	1300867	609	1301132
430	1300311	514	1300601	610	1300801
431	1300559	515	1300656	611	1300753
432	1300542	516	1300765	612	1300746
433	1300223	517	1300903	615	1300772
434	1300413	518	1301102	616	1301130
435	1300489	519	1300849	617	1301073
436	1300226	520	1300848	618	1300898
437	1300433	522	1300924	619	1300714
438	1300329	523	1301072	620	1301104
440	1300462			621	1300793
441	1300502			622	1301066
442	1300468			623	1300810
443	1300218			624	1300739
444	1300360				
445	1300309				
446	1300424				
447	1300457				
448	1300439				
449	1300514				
450	1300498				
464	1300344				

Exhibit 14a

Cohort 1
Pre-Study Medication Use

Subject Number	Medication
100	Prednisone Chlorambucil Atenolol Lisinopril
101	None
102	None
200	Lopid Atenolol Maxzide Premarin Baby aspirin FiberCon
201	Claritin Tylenol Allergy Sinus
202	Allergy shot (dust, mold) OTC sinus medication Cotrim
203	Capozide
204	None
300	None
301	Premarin Vitamins C & E
302	Hydropres

Exhibit 14b

Cohort 2
Pre-Study Medication Use

Subject Number	Medication
120	None
121	Insulin Cough drops
220	Insulin Cardura
221	None
320	Multivitamin Vitamin C
321	Hydrochlorothiazide

Exhibit 14c

Cohort 3
Pre-Study Medication Use

Subject Number	Medication
400	Zovirax Phentermine Fenfluramine Tri-Levlen
401	Synthroid Premarin
402	Tagamet
403	Betagan
404	Ibuprofen
405	Synthroid Paxil Zantac
406	None
407	Ventolin
408	None
409	None

Exhibit 14d

Cohort 4
Pre-Study Medication Use

Subject Number	Medication
420	Multivitamin Aspirin
421	None
423	Citrate with Vitamin D Motrin K-Nol Micro-K Hydrochlorothiazide
424	None
425	Aspirin Isosorbide Atenolol Zocor Norvasc
426	Darvocet
427	Multivitamin
428	Estrogen Relafen
429	None
430	None
431	None
432	None
433	Feostat Valium

Exhibit 14d (cont'd)

Cohort 4
Pre-Study Medication Use

Subject Number	Medication
434	None
435	Advil Aleve
436	None
437	LoOvral
438	None
440	Estrogen Premarin Bladder control pill Sinus medications Centrum Calcium supplement Vitamin C Healthy Trend (dietary supplement)
441	Premarin Estrogen
442	Estrogen Centrum Slo-Bid Aspirin Vitamin E Tylenol
443	None
444	Ventolin Ortho Cyclan
445	None

Exhibit 14d (cont'd)

Cohort 4
Pre-Study Medication Use

Subject Number	Medication
446	None
447	None
448	Monopril Paxil Buspar
449	Ventolin Azmacort Serevent
450	None
464	None

Exhibit 14e

Cohort 5
Pre-Study Medication Use

Subject Number	Medication
500	Naprosyn
501	Benadryl
502	Herbal allergy Tagamet
506	Benemid Colchicine Ibuprofen
507	Prozac Aspirin
508	None
509	Maxide Mega vitamins
510	Vitamins E, C, calcium Premarin Propranolol Synthroid
511	Claritin D Centrum vitamin
513	Vicodin PRN Tylenol PRN
514	None
515	Aspirin 3x week Zestril

Exhibit 14e - (cont'd)

Cohort 5
Pre-Study Medication Use

Subject Number	Medication
516	Norvasc Aspirin Calcium
517	Excedrin
518	Aspirin Gaviscon PRN
519	Depakote Tylenol
520	Humulin U Glucotrol Aspirin
521	Wellbutrin Clonopin
522	Advil
523	None

Exhibit 14f

Cohort 6
Pre-Study Medication Use

Subject Number	Medication
600	Maalox Extra Strength Tablets PRN Tylenol PRN Aspirin PRN
601	Norvasc Hytrin Synthroid Proventil
602	Zoloft Lorazepam Tylenol
603	None
605	Insulin humulin Hydrochlorothiazide Aspirin
606	Coumadin Lasix Cordarone Lanoxin Vasotec Synthroid
607	None
608	Remeron
609	Birth control pill Vitamins
610	Baby aspirin Ibuprofen

Exhibit 14f - (cont'd)

Cohort 6
Pre-Study Medication Use

Subject Number	Medication
611	None
612	Buspar Claritin Tylenol
615	None
616	Prempro
617	None
618	Inderal Hydrodiuril Mevacor Cardura Ibuprofen Lortab
619	None
620	None
621	Orthocyclen
622	Timolol Pred G Atropine Sulfate
623	Tylenol cold
624	Zoloft Darvocet